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(54) Title: ENZYMATIC ENCODING METHODS FOR EFFICIENT SYNTHESIS OF LARGE LIBRARIES

(57) Abstract: Disclosed is a method for obtaining a bifunctional complex comprising a molecule linked to a single stranded identifier oligonucleotide, wherein a nascent bifunctional complex comprising a chemical reaction site and a priming site for enzymatic addition of a tag is a) reacted at the chemical reaction site with one or more reactants, and b) reacted enzymatically at the priming site with one or more tag(s) identifying the reactant(s).

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Enzymatic encoding methods for efficient synthesis of large libraries

This application is a non-provisional of U.S. provisional application Serial No. 60/741,490 filed on December 2, 2005, which is hereby incorporated by reference in its entirety. All patent and non-patent references cited in U.S. provisional application Serial No. 60/741,490, or in the present application, are also hereby incorporated by reference in their entirety.

Technical Field of the Invention

The present invention relates to bifunctional complexes and methods for synthesising such complexes, as well as to methods for split-and-mix synthesis of different molecules each linked to a single stranded identifier oligonucleotide comprising a plurality of tags identifying the molecule and/or the chemical entities having participated in the synthesis of the molecule. The invention also relates to a method for generating a library of different bifunctional complexes and methods for selecting molecules and/or identifying molecules having a desirable property, such as affinity for a target compound.

Background of the Invention

Synthesis methods known as split-and-mix, or split-and-recombine, are known and have been used for the synthesis of different molecules. Split-and-mix methods for synthesising polypeptides and other biochemical polymers have been disclosed e.g. in US 5,723,598 directed to the generation of a library of bifunctional complexes comprising a polypeptide and an identifier oligonucleotide comprising tags in the form of a sequence of nucleotides identifying the amino acids which participated in the formation of the polypeptide. The methods are directed to chemical linkage of tags and do not disclose enzymatic linkage, such as ligation, of the nucleotide tags making up the identifier oligonucleotide.

WO 00/23458 discloses a split-and-mix method in which nucleic acid tags are involved in both molecule synthesis and molecule identification.

WO 2004/039825 and WO 2005/058479 disclose split-and-mix methods wherein tags in the form of identifier oligonucleotides are linked enzymatically. The prior art

methods do not disclose ligation of a double-stranded oligonucleotide substrate comprising a plurality of tags and complementary anti-tags at least partly hybridised to each other, wherein said ligation results in the formation of an identifier oligonucleotide comprising a plurality of consecutive nucleotides in the form of covalently linked tags, whereas the anti-tags of the double-stranded oligonucleotide substrate are not affected by the action of the ligase, i.e. no anti-tags become covalently linked as a result of the enzymatic ligation of the tag part of the double-stranded oligonucleotide substrate.

Reference is also made to WO2006/053571 disclosing methods for molecule synthesis.

Summary of the Invention

There is a need for improved methods for split-and-mix synthesis of libraries of small molecules for e.g. pharmaceutical and other purposes. The small molecules can initially be synthesised as part of a bifunctional complex further comprising an identifier oligonucleotide identifying the reactants which have participated in the synthesis of the small molecule.

The methods of the present invention employs a ligation step wherein the substrate for the ligase is in a double stranded form and wherein the substrate comprises a plurality of tags and at least one or more anti-tags wherein tags and anti-tag(s) is/are at least partly hybridised to each other. The tags are covalently linked as a result of the action of an enzyme comprising a ligase activity on the double stranded substrate, but no anti-tags are covalently linked as a result of said ligase action.

The method facilitates separation of ligated tags and discrete, non-ligated anti-tags because of the size and molecular weight difference between (i) the afore-mentioned single stranded identifier oligonucleotide comprising a plurality of covalently linked tags and (ii) discrete, non-ligated anti-tags. The identifier oligonucleotide comprising the ligated tags will typically have a length at least about 3 times the length of the individual anti-tags.

In one embodiment, the tags comprise a 5' phosphate, or a variant ligatable reactive group, whereas anti-tags do not. Therefore, the growing bifunctional complex will comprise a covalently linked "top"- strand to which a number, such as one or more,

of shorter and non-ligated anti-tag(s) is/are hybridised/annealed. This enables removal of anti-tag(s), e.g. after all tag additions have been performed (Fig. 1) or after each tag addition has been performed (Fig. 6).

Removal of anti-tags generally increases fidelity and allows extension after purification of the single-stranded oligonucleotide identifier comprising a plurality of ligated tags. Said extension makes possible the use of selection-specific sequences, which improves robustness towards contamination, which is a well-known phenomena when e.g. PCR amplifications are performed. Also, diversification-sequences can be used which diversifies otherwise un-distinguishable tag combinations. This makes it possible to identify tag combination sequences which may arise during PCR from a single tag combination. It is advantageous to identify such sequences as they may otherwise be interpreted as arising from several molecular entities containing the same tag combination, thus indicating that the specific tag combination corresponds to a small molecule with relatively high ability to be retained during subsequent selection procedures.

Also, because of the design of the tags, cross-hybridization between single stranded tags can be reduced or essentially eliminated. This greatly improves the purification process of the bifunctional complexes comprising single stranded identifier oligonucleotides following the synthesis reactions. One problem associated with purification of bifunctional complexes comprising double stranded identifier oligonucleotides is that such identifiers are prone to illegitimate hybridization when renaturing conditions are resumed following a purification process under denaturing conditions.

In order to achieve a minimum degree of cross-hybridization between tags in an identifier oligonucleotide, the tags can be designed using a computer algorithm to maximize or optimize the number of mismatches between any oligo pair, e.g. resulting in a minimum of seven mismatches between any two tag tags. This maximizes or optimize fidelity of hybridization and enables use of sorting methods, such as the ones disclosed e.g. in WO 00/23458 (Harbury). Moreover, it increases robustness of decoding by sequencing, e.g. the tag information can be decoded even if sequencing errors occur.

It is also possible to perform a quenching reaction with the reactants and tags. After reactant reactions resulting in the synthesis of the molecule, excess reactants are rendered un-reactive, e.g., by adding a quencher in the form e.g. of a reactant which reacts with excess reactants, e.g. by raising pH, etc, or by removal of a reactant which is critical for the reaction, etc. This can be done e.g. prior to, after or in parallel with deprotection of reacted reactants.

The same principle can be applied to the tags. Unreacted tags can be rendered unreactive at one or more tag reaction site(s), e.g., by dephosphorylation of tags containing 5' phosphates. Advantages associated with these steps include higher fidelity and the possible omission of purification steps between reaction cycles.

The same principle can also be applied to the chemical reaction site on the growing complexes.

In one embodiment of the present invention there is provided a method for the synthesis of a bifunctional complex comprising a molecule and a single stranded oligonucleotide identifier attached to the molecule, said method comprising the steps of

i) providing a display oligonucleotide attached to

a) one or more chemical reaction site(s) comprising one or more reactive groups and

b) one or more priming site(s) for enzymatic addition of a tag,

ii) providing a first reactant comprising one or more chemical entities and one or more reactive groups capable of reacting with

c) the one or more chemical reaction site(s) of the display oligonucleotide, and/or

d) one or more reactive groups of at least a first further reactant comprising one or more chemical entities, wherein said first further

reactant is provided simultaneously or sequentially in any order with the first reactant,

iii) providing a first oligonucleotide tag capable of hybridising to part of a first oligonucleotide anti-tag, wherein the first oligonucleotide tag identifies the first reactant and, optionally, the further first reactant,

iv) providing a first oligonucleotide anti-tag capable of hybridising to at least part of the first oligonucleotide tag provided in step iii) and to at least part of the display oligonucleotide provided in step i),

v) reacting the first reactant provided in step ii) with c) the one or more chemical reaction site(s) of the display oligonucleotide and/or with d) the one or more reactive groups of the first further reactant comprising one or more chemical entities,

wherein the reaction of complementary reactive groups result in the formation of a covalent bond, and

wherein one or more reactive group reactions of step v) result in the formation of one or more covalent bond(s) between the one or more chemical reaction site(s) of the display oligo and at least one chemical entity of at least one reactant selected from the group consisting of the first reactant and the further first reactant,

vi) hybridising the anti-tag to the display oligonucleotide and to the first oligonucleotide tag,

wherein method steps v) and vi) are simultaneous or sequential in any order,

vii) enzymatically ligating the display oligonucleotide and the first oligonucleotide tag,

viii) providing a second reactant comprising one or more chemical entities and one or more reactive groups capable of reacting with

c) the one or more chemical reaction site(s) of the display oligonucleotide, and/or

d) one or more reactive groups of one or more reactant(s) having reacted in a previous synthesis round, and/or

e) one or more reactive groups of a second further reactant comprising one or more chemical entities, wherein said second further reactant is provided simultaneously or sequentially in any order with the second reactant,

ix) providing a second oligonucleotide tag capable of hybridising to part of a second oligonucleotide anti-tag, wherein the second oligonucleotide tag identifies the second reactant and, optionally, the further second reactant,

x) providing a second oligonucleotide anti-tag capable of hybridising to part of the first oligonucleotide tag provided in step iii) and to part of the second oligonucleotide tag provided in step ix),

xi) reacting the second reactant provided in step viii) with c) the one or more chemical reaction site(s) of the display oligonucleotide and/or d) one or more reactive groups of one or more reactant(s) having reacted in a previous synthesis round and/or e) one or more reactive groups of a further second reactant comprising one or more chemical entities,

wherein the reaction of complementary reactive groups result in the formation of a covalent bond, and

wherein one or more reactive group reactions of step xi) result in

f) the formation of one or more covalent bond(s) between the one or more chemical reaction site(s) and at least one chemical entity of at least one reactant selected from the group consisting of the second reactant and the further second reactant, and/or

g) the formation of one or more covalent bond(s) between a reactant having reacted in a previous synthesis round and at least one chemical entity of at least one reactant selected from the group consisting of the second reactant and the further second reactant,

xii) hybridising the anti-tag to the first oligonucleotide tag and the second oligonucleotide tag,

wherein method steps xi) and xii) are simultaneous or sequential in any order,

xiii) enzymatically ligating the first and second oligonucleotide tags in the absence of ligation the first and second anti-tag oligonucleotides, and optionally

xiv) displacing unligated anti-tags from the bifunctional complex comprising a molecule and a single stranded oligonucleotide identifier comprising tags identifying the reactants which participated in the synthesis of the molecule.

It is clear from the above that the claimed method for synthesis of a bifunctional molecule covers a number of alternative embodiments – as well as combinations of a number of such aklternative embodiments. The below overview aim to specifically disclose a number of alternative embodiments and combinations thereof.

In step ia) there is provided a display oligonucleotide. In one embodiment the display oligonucleotide has one chemical reaction site comprising one or more reactive groups. A chemical reaction site comprising more than one reactive group can be used for the synthesis of both linear molecules, branched molecules, cyclical molecules and the chemical reaction site can be in the form of a scaffold for the synthesis of small, scaffolded molecules.

In another embodiment, the display oligonucleotide has more than one chemical reaction site each comprising one or more reactive groups.

For each of the above alternatives the display oligonucleotide can have one or more priming sites. Accordingly, as far as step i) is concerned, the following alternatives are provided:

A display oligonucleotide comprising one chemical reaction site and one priming site;
A display oligonucleotide comprising more than one chemical reaction site and one priming site;
A display oligonucleotide comprising one chemical reaction site and more than one priming site; and
A display oligonucleotide comprising more than one chemical reaction site and more than one priming site.

Each of the above-mentioned sites can have one or more reactive groups. When more sites are provided, there is also provided an embodiment wherein one site has one reactive group whereas the remaining sites have more than one reactive group.

In step ii) there is provided a first reactant comprising one or more chemical entities, wherein each entity has one or more reactive groups. Accordingly, as far as step ii) is concerned, the following alternatives are provided:

A first reactant comprising one chemical entity having one reactive group;
A first reactant comprising more than one chemical entity each having one reactive group;
A first reactant comprising one chemical entity each having more than one reactive group; and
A first reactant comprising more than one chemical entity each having more than one reactive group.

In one embodiment, a display oligonucleotide selected from the group consisting of a display oligonucleotide comprising one chemical reaction site and one priming site; a display oligonucleotide comprising more than one chemical reaction site and one priming site; a display oligonucleotide comprising one chemical reaction site and more than one priming site; and a display oligonucleotide comprising more than one chemical reaction site and more than one priming site, is reacted with a first reactant selected from the group consisting of a first reactant comprising one

chemical entity having one reactive group; a first reactant comprising more than one chemical entity each having one reactive group; a first reactant comprising one chemical entity each having more than one reactive group; and a first reactant comprising more than one chemical entity each having more than one reactive group.

Step ii) also allows a reaction to occur between a first reactant and a further first reactant, wherein the reaction product reacts, simultaneously or sequentially in any order, with a chemical reaction site of a display molecule. Accordingly, there is also provided in step ii):

A first further reactant comprising one chemical entity having one reactive group;
A first further reactant comprising more than one chemical entity each having one reactive group;
A first further reactant comprising one chemical entity having more than one reactive group; and
A first further reactant comprising more than one chemical entity each having more than one reactive group.

Consequently, there is provided in one embodiment a reaction between a first reactant selected from the group consisting of a first reactant comprising one chemical entity having one reactive group; a first reactant comprising more than one chemical entity each having one reactive group; a first reactant comprising one chemical entity having more than one reactive group; and a first reactant comprising more than one chemical entity each having more than one reactive group, and a first further reactant selected from the group consisting of a first further reactant comprising one chemical entity having one reactive group; a first further reactant comprising more than one chemical entity each having one reactive group; a first further reactant comprising one chemical entity having more than one reactive group; and a first further reactant comprising more than one chemical entity each having more than one reactive group.

In step viii) there is provided a second reactant comprising one or more chemical entities, wherein each entity has one or more reactive groups. Accordingly, as far as step ii) is concerned, the following alternatives are provided:

A second reactant comprising one chemical entity having one reactive group;
A second reactant comprising more than one chemical entity each having one reactive group;
A second reactant comprising one chemical entity each having more than one reactive group; and
A second reactant comprising more than one chemical entity each having more than one reactive group.

In one embodiment, a display oligonucleotide selected from the group consisting of a display oligonucleotide comprising one chemical reaction site and one priming site; a display oligonucleotide comprising more than one chemical reaction site and one priming site; a display oligonucleotide comprising one chemical reaction site and more than one priming site; and a display oligonucleotide comprising more than one chemical reaction site and more than one priming site, wherein one or more chemical reaction sites have reacted with one or more reactants in a first or previous reaction round, is reacted with a second reactant selected from the group consisting of a second reactant comprising one chemical entity having one reactive group; a second reactant comprising more than one chemical entity each having one reactive group; a second reactant comprising one chemical entity each having more than one reactive group; and a second reactant comprising more than one chemical entity each having more than one reactive group.

Step viii) also allows a reaction to occur between a second reactant and a further second reactant, wherein the reaction product reacts, simultaneously or sequentially in any order, with a chemical reaction site of a display molecule, or a reactive group of a reactant having reacted with one or more chemical reaction sites of the display oligonucleotide in a previous reaction round. Accordingly, there is also provided in step viii):

A second further reactant comprising one chemical entity having one reactive group;
A second further reactant comprising more than one chemical entity each having one reactive group;
A second further reactant comprising one chemical entity having more than one reactive group; and
A second further reactant comprising more than one chemical entity each having more than one reactive group.

Consequently, there is provided in one embodiment a reaction between a second reactant selected from the group consisting of a second reactant comprising one chemical entity having one reactive group; a second reactant comprising more than one chemical entity each having one reactive group; a second reactant comprising one chemical entity having more than one reactive group; and a second reactant comprising more than one chemical entity each having more than one reactive group, and a second further reactant selected from the group consisting of a second further reactant comprising one chemical entity having one reactive group; a second further reactant comprising more than one chemical entity each having one reactive group; a second further reactant comprising one chemical entity having more than one reactive group; and a second further reactant comprising more than one chemical entity each having more than one reactive group.

In one embodiment, a reactant having reacted in a previous reaction round with one or more chemical reaction sites of a display oligonucleotide, or a reactant having previously reacted with a reactant having reacted with said one or more chemical reaction sites, is to be regarded as a chemical reaction site capable of reacting with one or more reactants provided in a subsequent reaction round.

When a library of different bifunctional complexes are synthesised by split-and-mix methods according to the present invention, the composition of nascent bifunctional complexes obtained in step vii) is split (divided) into a plurality of different compartments. In each different compartment, a different second reactant is provided, c.f. step viii) above. Also, in each different compartment a second oligonucleotide tag is added, c.f. step ix) above, said second oligonucleotide tag identifying in each different compartment the second reactant, and optionally also the further second reactant, provided in the same compartment as the second oligonucleotide tag.

In each different compartment a suitable anti-tag is provided, c.f. step x) above, and hybridised to at least partly complementary tags, c.f. step xii) above.

The reaction cited in step xi) herein above takes place in each different compartment, resulting in the synthesis in each different compartment of different nascent bifunctional complexes comprising the result (reaction product in the form of

a molecule or molecule precursor) of a reaction involving the first and second reactants, and optionally also the further first reactant and/or the further second reactant, wherein said reaction product of the nascent bifunctional product is linked to a corresponding identifier oligonucleotide comprising the first and second oligonucleotide tags, c.f. step xiv). At the end of each synthesis round, the generated, nascent or final bifunctional complex is optionally separated from unligated anti-tags. However, this separation step can also be carried out only once, after the final synthesis round.

The different bifunctional complexes from a given round of synthesis are combined and split in order to initiate a new synthesis round, c.f. steps viii) to xii) above, which are repeated for a different reactant and optionally a different further reactant.

Taking the above library synthesis steps into consideration, the present invention is in one embodiment directed to a method for the synthesis of a plurality of different bifunctional complexes, said method comprising the steps of

i) providing a plurality of display oligonucleotides each attached to

a) one or more chemical reaction site(s) comprising one or more reactive groups and

b) one or more priming site(s) for enzymatic addition of a tag,

ii) providing a plurality of first reactants each comprising one or more chemical entities and one or more reactive groups, each first reactant being capable of reacting with

c) the one or more chemical reaction site(s) of the display oligonucleotide, and/or

d) one or more reactive groups of a first further reactant comprising one or more chemical entities, wherein said first further reactant is provided simultaneously or sequentially in any order with the first reactant,

iii) providing a plurality of first oligonucleotide tags each capable of hybridising to part of a first oligonucleotide anti-tag, wherein each first oligonucleotide tag identifies a first reactant and, optionally, a further first reactant,

iv) providing a plurality of first oligonucleotide anti-tags each capable of hybridising to at least part of a first oligonucleotide tag provided in step iii) and to at least part of a display oligonucleotide provided in step i),

v) reacting each of the first reactants provided in step ii) with c) the one or more chemical reaction site(s) of the display oligonucleotides and/or with d) the one or more reactive groups of a first further reactant comprising one or more chemical entities,

wherein the reaction of complementary reactive groups result in the formation of a covalent bond, and

wherein one or more reactive group reactions of step v) result in the formation of one or more covalent bond(s) between the one or more chemical reaction site(s) of the display oligonucleotides and at least one chemical entity of at least one reactant selected from the group consisting of a first reactant and a further first reactant,

vi) hybridising anti-tags to display oligonucleotides and to first oligonucleotide tags,

wherein method steps v) and vi) are simultaneous or sequential in any order,

vii) enzymatically ligating display oligonucleotides and first oligonucleotide tags,

viii) dividing the plurality of nascent bifunctional complexes obtained in step vii) into a plurality of different compartments,

ix) providing in each different compartment a plurality of different second reactants each comprising one or more chemical entities and one or more reactive groups capable of reacting with

c) the one or more chemical reaction site(s) of each of the display oligonucleotides, and/or

d) one or more reactive groups of one or more reactant(s) having reacted in a previous synthesis round, and/or

e) one or more reactive groups of a second further reactant comprising one or more chemical entities, wherein said second further reactants are provided simultaneously or sequentially in any order with the second reactants,

x) providing in each different compartment a plurality of second oligonucleotide tags each capable of hybridising to part of a second oligonucleotide anti-tag, wherein different second oligonucleotide tags are provided in each different compartment, and wherein each different second oligonucleotide identifies a different second reactant and, optionally, a further second reactant which may be the same or a different further second reactant in each different compartment,

xi) providing in each different compartment a plurality of second oligonucleotide anti-tags capable of hybridising to part of a first oligonucleotide tag provided in step iii) and to part of a second oligonucleotide tag provided in step x),

xii) reacting in each different compartment each of the different second reactants provided in step ix) with c) the one or more chemical reaction site(s) of a display oligonucleotide and/or d) one or more reactive groups of one or more reactant(s) having reacted in a previous synthesis round and/or e) one or more reactive groups of a further second reactant comprising one or more chemical entities,

wherein said one or more reactions result in the formation of different bifunctional complexes in each different compartment,

wherein the reaction of complementary reactive groups result in the formation of a covalent bond, and

wherein one or more reactive group reactions of step xii) result in

f) the formation of one or more covalent bond(s) between the one or more chemical reaction site(s) and at least one chemical entity of at least one reactant selected from the group consisting of second reactants and further second reactants, and/or

g) the formation of one or more covalent bond(s) between a reactant having reacted in a previous synthesis round and at least one chemical entity of at least one reactant selected from the group consisting of second reactants and further second reactants,

xiii) hybridising anti-tags to first oligonucleotide tags and second oligonucleotide tags in each different compartment,

wherein method steps xii) and xiii) are simultaneous or sequential in any order,

xiv) enzymatically ligating in each different compartment first and second oligonucleotide tags in the absence of ligation first and second anti-tag oligonucleotides, and optionally

xv) displacing in each compartment unligated anti-tags from bifunctional complexes comprising a molecule and a single stranded oligonucleotide identifier comprising tags identifying the one or more reactants which participated in the synthesis of the molecule.

The above steps viii) to xv) can be repeated once or more than once using different reactants and tags identifying said different reactants. Prior to the repetition of the

afore-mentioned steps the synthesised bifunctional complexes are combined and split into different reaction compartments.

As will be clear from the above, the present invention in one embodiment allows for efficient, enzymatic ligation of a plurality of single-stranded tags making up one strand only of an at least partly double stranded, identifier oligonucleotide hybridisation complex (at least at the time of ligation), wherein anti-tags at least partly hybridised to the tags are not ligated and can easily be disposed of after each synthesis round (figure 6) or after molecule synthesis have been completed (figure 1).

None of the prior art methods disclose the formation of a double stranded, identifier oligonucleotide precursor comprising complementary tags and anti-tags which are at least partly hybridised to each other, but not covalently linked. That is, prior to ligation, a tag can initially be hybridised to an anti-tag of the complementary strand of the double stranded, identifier oligonucleotide precursor, but not covalently linked to either such an anti-tag, or to another tag forming part of the same strand of the double stranded, identifier oligonucleotide precursor.

Likewise, an anti-tag can initially be hybridised to a tag of the complementary strand of the double stranded, identifier oligonucleotide precursor, but not covalently linked to either such a tag, or to another anti-tag forming part of the same strand of the double stranded, identifier oligonucleotide precursor.

In a further aspect of the invention there is provided a method for obtaining a bifunctional complex comprising a molecule and an identifier oligonucleotide. Initially, a nascent bifunctional complex comprising one or more chemical reaction site(s) and one or more priming site(s) for enzymatic addition of a tag is reacted a) at the chemical reaction site with one or more reactant(s) in the form of chemical entities and b) reacted at the priming site with one or more identifier oligonucleotide tag(s) identifying the reactant(s) which have reacted - or are going to react - with each other and/or with the chemical reaction site, wherein tag ligation results in the formation only of a single stranded identifier oligonucleotide comprising a plurality of tags, whereas no anti-tag at least partly hybridised the one or more tags are ligated to a neighbouring anti-tag.

There is also provided a bifunctional complex as disclosed herein. In one aspect, the bifunctional complex is an intermediate bifunctional complex comprising a molecule precursor and a single stranded identifier oligonucleotide identifying the molecule precursor, wherein the single stranded identifier comprises a plurality of covalently linked tags which are at least partly hybridised to one or more corresponding anti-tag(s), wherein, when more anti-tags are present, said anti-tags are not covalently linked to each other.

In another aspect there is provided a bifunctional complex comprising a molecule and a single stranded identifier oligonucleotide identifying the molecule, wherein the single stranded identifier comprises a plurality of covalently linked tags which are at least partly hybridised to one or more corresponding anti-tag(s), wherein, when more anti-tags are present, said anti-tags are not covalently linked.

In a still further aspect there is provided a bifunctional complex comprising a molecule and a single stranded identifier oligonucleotide identifying the molecule, wherein the single stranded identifier comprises a plurality of covalently linked tags.

There is also provided a method for synthesising a library of different bifunctional complexes. The lack of a covalent link between a reactant and a tag means that a library can be produced by a split-and-mix strategy. In a first step a display oligonucleotide or a nascent bifunctional complex is dispensed in separate compartments and subsequently exposed to a different reactant in each or at least the majority of the compartments. The reactant reacts in each compartment with at least one reactive group of the chemical reaction site and a tag identifying the reactant is added by enzymatic action at the priming site. In one embodiment of the invention, the tag is added to the priming site by enzymatic ligation.

There is also provided a method for partitioning a library or composition of different bifunctional complexes, said partitioning resulting in the selection of bifunctional complexes comprising molecules having one or more desirable characteristics. The partitioning of bifunctional complexes can occur as a result of the differential affinity of the molecule(s) of different bifunctional complexes for the same or different targets, such as the targets disclosed herein. Alternatively, and/or in combination with the above, partitioning of bifunctional complexes can occur based on tag

features, such as e.g. tag nucleotide sequences and/or physical properties capable of distinguishing different tags and/or identifier oligonucleotides from each other.

Whereas an initially generated library is often termed a "naïve library", the library obtained after partitioning is often termed an "intelligent" or "enriched" library. The partitioning can be carried out once or more than once using the same or different partitioning parameters, such as binding affinity to a target compound under predetermined assaying conditions.

In a further aspect there is provided a pharmaceutical composition comprising the molecule, or a variant of the molecule, of the bifunctional complex – wherein preferably the molecule is not linked to the identifier oligonucleotide of the bifunctional complex. The terms "molecule", "compound", "chemical compound", "reaction product", "bioactive agent" and "bioactive species" are used interchangably herein when referring to a product obtained by the methods of the present invention, or a variant of such a product obtained e.g. when a "lead compound" or "drug lead" is being optimised for pharmaceutical uses. A "bioactive agent" or a "bioactive species" is typically a molecule which exerts a biologically relevant activity, such as e.g. a biologically relevant binding affinity for a target compound.

There is also provided the use of a bifunctional complex according to the invention in the manufacture of a medicament for the treatment of a clinical indication in an individual in need thereof.

Definitions

α-peptide: Peptide comprising or essentially consisting of at least two □-amino acids linked to one another by a linker including a peptide bond.

Amino acid: Entity comprising an amino terminal part (NH_2) and a carboxy terminal part (COOH) separated by a central part comprising a carbon atom, or a chain of carbon atoms, comprising at least one side chain or functional group. NH_2 refers to the amino group present at the amino terminal end of an amino acid or peptide, and COOH refers to the carboxy group present at the carboxy terminal end of an amino acid or peptide. The generic term amino acid comprises both natural and non-natural amino acids. Natural amino acids of standard nomenclature as listed in J.

Biol. Chem., 243:3552-59 (1969) and adopted in 37 C.F.R., section 1.822(b)(2) belong to the group of amino acids listed herein below. Non-natural amino acids are those not listed in the below table. Examples of non-natural amino acids are those listed e.g. in 37 C.F.R. section 1.822(b)(4), all of which are incorporated herein by reference. Further examples of non-natural amino acids are listed herein below. Amino acid residues described herein can be in the "D" or "L" isomeric form.

Symbols		Amino acid
1-Letter	3-Letter	
Y	Tyr	tyrosine
G	Gly	glycine
F	Phe	phenylalanine
M	Met	methionine
A	Ala	alanine
S	Ser	serine
I	Ile	isoleucine
L	Leu	leucine
T	Thr	threonine
V	Val	valine
P	Pro	proline
K	Lys	lysine
H	His	histidine
Q	Gln	glutamine
E	Glu	glutamic acid
W	Trp	tryptophan
R	Arg	arginine
D	Asp	aspartic acid
N	Asn	asparagine
C	Cys	cysteine

Amino acid precursor: Moiety capable of generating an amino acid residue following incorporation of the precursor into a peptide.

Amplifying: Any process or combination of process steps that increases the number of copies of an identifier oligonucleotide. Amplification of identifier oligonucleotides can be carried out by any state of the art method including, but not limited to, a polymerase chain reaction to increase the copy number of each identifier oligonucleotide by using the identifier oligonucleotide(s) as template(s) for synthesising additional copies of the identifier oligonucleotides. Any amplification reaction or combination of such reactions known in the art can be used as appropriate as readily recognized by those skilled in the art. Accordingly, identifier oligonucleotides can be amplified using a polymerase chain reaction (PCR), a ligase chain reaction (LCR), by in vivo amplification of identifier oligonucleotides cloned in DNA chromosomal or extra-chromosomal elements including vectors and plasmids, and the like. The amplification method should preferably result in the proportions of the amplified mixture of identifier oligonucleotides being essentially representative of the proportions of identifier oligonucleotides of different sequences in a mixture prior to said amplification.

Base: Nitrogeneous base moiety of a natural or non-natural nucleotide, or a derivative of such a nucleotide comprising alternative sugar or phosphate moieties. Base moieties include any moiety that is different from a naturally occurring moiety and capable of complementing one or more bases of the opposite nucleotide strand of a double helix.

Bifunctional complex: Molecule linked to an identifier oligonucleotide capable of identifying the molecule and/or the reactants having participated in the synthesis of the molecule. An “intermediate bifunctional complex” wherein the chemical reaction site or the (precursor) molecule part will undergo further reactions with reactants or chemical entities in order to synthesise a “final” molecule is also termed a “nascent bifunctional complex”.

Binding region: Region on a string of consecutive nucleotides to which an enzyme can bind, e.g. when ligating different oligonucleotides (e.g. in case of a ligase) or prior to a fill-in reaction (e.g. in case of a polymerase).

Catalyst: Moiety acting on a starting compound or a set of starting compounds and speeding up chemical reactions involving such compound(s).

Chemical entity: Functional chemical group, or reactant, which, when reacted, becomes covalently attached to a site, such as a chemical reaction site, for example a site on a molecule, such as a scaffold at which site one or more reactive groups can be e.g. reacted, substituted or added. Chemical entities and reactants are used interchangably herein in bond-forming reactions resulting in the formation of a molecule, or a molecule precursor. For example, a carbon atom that is part of the scaffold can be bound to a methyl group chemical entity. This site may also be within the scaffold; for example, a hydrogen atom on a carbon atom within a ring can be a chemical entity. Chemical entities can preferably be modified or replaced by other chemical entities or derived substituents using one step or two step chemical processes. Protection and de-protection steps may also be required. In an embodiment of the methods of the invention, this modification can be done independently at each chemical entity, without the need to add protecting groups at the other chemical entities. Chemical entities may comprise substituents capable of anomalous scattering. The chemical entity either forms part of a reactant or is used herein interchangably with the term “reactant”. The chemical entity can comprise or be linked to a reactive group capable of reacting with reactive groups of other chemical entities or reactants. Chemical entities that can be used in some aspects of the present invention include, but are not limited to H, benzyl halide, benzyl alcohol, allyl halide, allyl alcohol, carboxylic acid, aryl amine, heteroaryl amine, benzyl amine, aryl alkyl amine, alkyl amino, phenol, aryl halide, heteroaryl halide, heteroaryl chloride, aryl aldehyde, heteroaryl aldehyde, aryl alkyl aldehyde, alkyl aldehyde, aryl, heteroaryl, alkyl, aryl alkyl, ketone, arylthiol, heteroaryl thiol, urea, imide, aryl boronic acid, ester, carbamate, tert-butyl carbamate, nitro, aryl methyl, heteroaryl methyl, vinyl methyl, 2- or 2,2-substituted vinyls, 2-substituted alkynes, acyl halide, aryl halide, alkyl halide, cycloalkyl halide, sulfonyl halide, carboxylic anhydride, epoxide, and sulfonic acid. In some embodiments, the chemical entities may include, but are not limited to benzyl bromide, benzyl alcohol, allyl bromide, allyl alcohol, carboxylic acid, aryl amine, heteroaryl amine, benzyl amine, aryl alkyl amine, phenol, aryl bromide, heteroaryl bromide, heteroaryl chloride, aryl aldehyde, heteroaryl aldehyde, aryl alkyl aldehyde, ketone, arylthiol, heteroaryl thiol, urea, imide, and aryl boronic acid. Halide may include, for example, iodide, bromide, fluoride, and chloride. Halide may include halides capable of anomalous scattering, such as, for example, bromide or iodide. By convention, a chemical entity can be considered as either "direct" chemical entities or "latent" chemical entities, with some having the capacity to function as either. A direct chemical entity is a

functional group or moiety that can react directly with another functional group or moiety without prior modification or that can be rendered reactive by the addition of reagents and/or catalysts typically, but not necessarily, in a single-pot reaction. Examples of a direct chemical entity include, but are not limited to: the Br in a benzyl bromide, carboxylic acid, amine, phenol, the Br in an aryl bromide, aldehyde, thiol, boronic acid or ester, and the like. A latent chemical entity is a functional group or moiety that requires prior modification, either in a separate step after which it may or may not be isolated, or generated in situ to afford a more reactive species (i.e., obtaining a direct chemical entity). A latent chemical entity may also comprise a moiety that by virtue of its proximity or connectivity to a functional group or other moiety is rendered reactive. Examples of a latent chemical entity include, but are not limited to: nitro (which can be reduced to an amine), aryl methyl (which can be converted to aryl bromomethyl or to aryl carboxylic acid), olefin (which can undergo oxidative cleavage to afford an epoxide, an aldehyde or carboxylic acid), and the like. The adoption of the above convention serves to illustrate the scope of chemical moieties regarded as chemical entities within the present invention. Additional chemical entities are within the scope of this invention and are evident to those trained in the art and having access to the chemical literature.

Chemical group: Entity of a reactant or chemical entity participating in the synthesis of a molecule.

Chemical reaction site: Site of a nascent bifunctional complex reacted with at least one reactant or chemical entity during the synthesis of a molecule.

Cleavable linker: Residue or bond capable of being cleaved under predetermined conditions.

Cleaving: Breaking a chemical bond. The bond can be a covalent bond or a non-covalent bond.

Complementary binding partners: Binding partners capable of reacting with each other. Binding partner and reactant are used interchangably herein.

Complementary reactive groups: Reactive groups capable of reacting with each other.

Contacting: Bringing e.g. corresponding reactive groups or corresponding binding partners or hybridization partners into reactive contact with each other. The reactive contact is evident from a reaction between the partners, or the formation of a bond, or hybridization, between the partners.

Cycle of reaction: The methods of the present invention employ split-n-mix strategies for molecule synthesis. A reaction cycle involves a reaction of a reactant or chemical entity with another reactant or chemical entity or with the chemical reaction site and the reaction of a tag with another tag or with the priming site. In other words, a reaction cycle involves both a molecule specific reaction and a tag specific reaction.

Enzyme: Any polypeptide capable of speeding up chemical reactions. Enzymes act as catalysts for a single reaction and converts a starting compound or a specific set of starting compounds into specific products. Examples are ligases and polymerases.

Hybridisation: The ability of complementary nucleotides to form an association through hydrogen bonding.

Identifier oligonucleotide: The identifier oligonucleotide can be single stranded or, in an initial state, at least partly hybridised to one or more discrete anti-tags. The oligonucleotide identifier(s) can be linear or branched. The nucleotides of the identifier oligonucleotide can be natural and/or non-natural nucleotides, including nucleotide derivatives. The length can vary as long as the identifier is long enough (i.e. contains a sufficient number of nucleotides) to identify the molecule part of the bifunctional complex to which the identifier oligonucleotide is linked, or the reactants having participated in the synthesis of the molecule.

Interacting: Used interchangably with contacting. Bringing species such as e.g. correspnding binding partners into reactive contact with each other. The reaction can be mediated by recognition groups forming corresponding binding partners by means of covalent or non-covalent bonds.

Library: A composition of different moieties, such as small molecules or bifunctional complexes comprising different small molecules each linked to a specific identifier oligonucleotide identifying the small molecule.

Linker: A residue or chemical bond separating at least two species. The species can be retained at an essentially fixed distance, or the linker can be flexible and allow the species some freedom of movement in relation to each other. The link can be a covalent bond or a non-covalent bond.

Molecule: A chemical reaction site, such as a scaffold, which has reacted with one or more reactants. The molecule can form part of a bifunctional complex further comprising an identifier oligonucleotide capable of identifying the molecule or the reactants which have reacted in the method for synthesising the molecule. The molecule is also termed a “display molecule”. The molecule part of the bifunctional complex can be linked covalently to the priming site of the bifunctional complex and/or to a single stranded identifier oligonucleotide comprising a plurality of covalently linked tags. A "molecule" is any chemical entity, or part thereof, selected or designed to be part of a synthetic precursor to lead candidate or drug candidate. The molecule comprises one, two, or three or more chemical substituents, also called "chemical entities". A molecule preferably exhibits properties of desirable lead compounds, including, for example, a low molecular complexity (low number of hydrogen bond donors and acceptors, low number of rotatable bonds, and low molecular weight), and low hydrophobicity. Because the molecule is small, one of ordinary skill in the art may further develop or elaborate the molecule into a lead or drug candidate by modifying the molecule, either at the chemical entities or at the core structure, to have desirable drug characteristics, including, for example, by meeting the Lipinski rule of five. Preferred molecule properties include lead-like properties and are known to those of ordinary skill in the art and are described in Teague, S. J., et al., Agnew. Chem. Int. Ed. 38:3743-3748, 1999; Oprea, T. I., et al., J. Chem. Inf. Comput. Sci. 41:1308-1315, 2001; and Hann, M. M. et al., J. Chem. Inf. Comput. Sci. 41:856-864, 2001. Desirable molecules include, but are not limited to, for example, molecules having many or all of the following general properties: MW<about 1000, MW<about 500, MW<about 350, MW<about 300, or MW<about 250, a clogP<about 3, less than about 5 rings, and an LogP<about 5 or <about 4. Other general properties may include less than about 15, such as 12, for example 10 nonterminal single bonds, less than about 10, such as 8, for example 6 hydrogen

bond donors, and less than about 10, such as 8, for example 6 hydrogen bond acceptors. Thus, molecules are designed so that more complexity and weight can be added during development and building out of the compound into a lead candidate, while maintaining the general properties. Molecules may comprise scaffolds comprising cyclic or non-cyclic structures. Examples of non-cyclic scaffolds, include, but are not limited to, hypusine, putrescine, gamma-aminobutyric acid, and 2-hydroxyputresine. Generally, the scaffold portion of a molecule may comprise 1) a cyclic structure, including any of the cyclic structures described herein, with 2) one or more of the chemical entities disclosed herein.

Nascent bifunctional complex: Also referred to as a growing complex; specifies an initial or intermediate complex to be processed according to the methods of the present invention. An intermediate complex designates an initial complex that has been subjected to one or more rounds of reactant reaction and tag addition.

Natural nucleotide: Any of the four deoxyribonucleotides, dA, dG, dT, and dC (constituents of DNA) and the four ribonucleotides, A, G, U, and C (constituents of RNA) are natural nucleotides. Each natural nucleotide comprises a sugar moiety (ribose or deoxyribose), a phosphate moiety, and a natural/standard base moiety. Natural nucleotides bind to complementary nucleotides according to well-known base pairing rules, such as e.g. Watson & Crick type base pairing, where adenine (A) pairs with thymine (T) or uracil (U); and where guanine (G) pairs with cytosine (C), wherein corresponding base-pairs are part of complementary, anti-parallel nucleotide strands. The base pairing results in a specific hybridization between predetermined and complementary nucleotides. The base pairing is the basis by which enzymes are able to catalyze the synthesis of an oligonucleotide complementary to the template oligonucleotide. In this synthesis, building blocks (normally the triphosphates of ribo or deoxyribo derivatives of A, T, U, C, or G) are directed by a template oligonucleotide to form a complementary oligonucleotide with the correct, complementary sequence. The recognition of an oligonucleotide sequence by its complementary sequence is mediated by corresponding and interacting bases forming base pairs. In nature, the specific interactions leading to base pairing are governed by the size of the bases and the pattern of hydrogen bond donors and acceptors of the bases. A large purine base (A or G) pairs with a small pyrimidine base (T, U or C). Additionally, base pair recognition between bases is influenced by hydrogen bonds formed between the bases. In the geometry of the

Watson-Crick base pair, a six membered ring (a pyrimidine in natural oligonucleotides) is juxtaposed to a ring system composed of a fused, six membered ring and a five membered ring (a purine in natural oligonucleotides), with a middle hydrogen bond linking two ring atoms, and hydrogen bonds on either side joining functional groups appended to each of the rings, with donor groups paired with acceptor groups.

Non-natural base pairing: Base pairing among non-natural nucleotides, or among a natural nucleotide and a non-natural nucleotide. Examples are described in US 6,037,120, wherein eight non-standard nucleotides are described, and wherein the natural base has been replaced by a non-natural base. As is the case for natural nucleotides, the non-natural base pairs involve a monocyclic, six membered ring pairing with a fused, bicyclic heterocyclic ring system composed of a five member ring fused with a six membered ring. However, the patterns of hydrogen bonds through which the base pairing is established are different from those found in the natural AT, AU and GC base pairs. In this expanded set of base pairs obeying the Watson-Crick hydrogen-bonding rules, A pairs with T (or U), G pairs with C, iso-C pairs with iso-G, and K pairs with X, H pairs with J, and M pairs with N (Figure 2). Nucleobases capable of base pairing without obeying Watson-Crick hydrogen-bonding rules have also been described (Berger et al., 2000, Nucleic Acids Research, 28, pp. 2911-2914).

Non-natural nucleotide: Any nucleotide not falling within the above definition of a natural nucleotide.

Nucleotide: The term nucleotides as used herein refers to both natural nucleotides and non-natural nucleotides. Nucleotides can differ from natural nucleotides by having a different phosphate moiety and/or a different sugar moiety and/or a different base moiety from the natural nucleotide. Accordingly, nucleotides can form part of an identifier oligonucleotide when they are linked to each other by a natural bond in the form of a phosphodiester bond, or a non-natural bond, such as e.g. a peptide bond as in the case of PNA (peptide nucleic acids).

Nucleotide derivative: Nucleotide further comprising an appended molecular entity. The nucleotides can be derivatized on the bases and/or the ribose/deoxyribose unit and/or the phosphate. Preferred sites of derivatization on the bases include the 8-

position of adenine, the 5-position of uracil, the 5- or 6-position of cytosine, and the 7-position of guanine. The nucleotide-analogs described below can be derivatized at the corresponding positions (Benner, United States Patent 6,037,120). Other sites of derivatization can be used, as long as the derivatization does not disrupt base pairing specificity. Preferred sites of derivatization on the ribose or deoxyribose moieties are the 5', 4' or 2' positions. In certain cases it can be desirable to stabilize the nucleic acids towards degradation, and it can be advantageous to use 2'-modified nucleotides (US patent 5,958,691). Again, other sites can be employed, as long as the base pairing specificity is not disrupted. Finally, the phosphates can be derivatized. Preferred derivatizations are phosphorothiote. Nucleotide analogs (as described below) can be derivatized similarly to nucleotides. It is clear that the various types of modifications mentioned herein above, including i) derivatization and ii) substitution of the natural bases or natural backbone structures with non-natural bases and alternative, non-natural backbone structures, respectively, can be applied once or more than once within the same nucleic acid molecule.

Oligonucleotide: The term oligonucleotide comprises oligonucleotides of both natural and/or non-natural nucleotides, including any combination thereof. The natural and/or non-natural nucleotides can be linked by natural phosphodiester bonds or by non-natural bonds. Oligonucleotides have at least 2 nucleotides, such as 3 or more nucleotides.

Oligomer: Molecule comprising a plurality of monomers that can be identical, of the same type, or different. Oligomers can be homooligomers comprising a plurality of identical monomers, oligomers comprising different monomers of the same type, or heterooligomers comprising different types of monomers, wherein each type of monomer can be identical or different.

Partitioning: Process whereby molecules, or complexes comprising such molecules linked to an identifier oligonucleotide, are preferentially bound to a target molecule and separated from molecules, or complexes comprising such molecules linked to an identifier oligonucleotide, that do not have an affinity for - and is consequently not bound to - such target molecules. Partitioning can be accomplished by various methods known in the art. The only requirement is a means for separating molecules bound to a target molecule from molecules not bound to target molecules under the same conditions. The choice of partitioning method will depend on

properties of the target and of the synthesised molecule and can be made according to principles and properties known to those of ordinary skill in the art.

Peptide: Plurality of covalently linked amino acid residues defining a sequence and linked by amide bonds. The term is used analogously with oligopeptide and polypeptide. The amino acids can be both natural amino acids and non-natural amino acids, including any combination thereof. The natural and/or non-natural amino acids can be linked by peptide bonds or by non-peptide bonds. The term peptide also embraces post-translational modifications introduced by chemical or enzyme-catalyzed reactions, as are known in the art. Such post-translational modifications can be introduced prior to partitioning, if desired. Amino acids as specified herein will preferentially be in the L-stereoisomeric form. Amino acid analogs can be employed instead of the 20 naturally-occurring amino acids. Several such analogs are known, including fluorophenylalanine, norleucine, azetidine-2-carboxylic acid, S-aminoethyl cysteine, 4-methyl tryptophan and the like.

Plurality: At least two.

Polymer: Molecules characterised by a sequence of covalently linked residues each comprising a functional group, including H. Polymers according to the invention comprise at least two residues.

Precursor entity: Chemical entity further comprising a precursor moiety which is cleaved or modified when the chemical entity is reacted with another chemical entity.

Priming site: Site on a display oligonucleotide or a nascent bifunctional complex to which at least on tag is added chemically or enzymatically or otherwise during the synthesis of the molecule. At least one tag is added enzymatically.

Reactive group: Part of a reactant and linked to the chemical entity of the reactant. Complementary reactive groups brought into reactive contact with each other are capable of forming a chemical bond linking two binding partners. Reaction of reactants comprising complementary reactive groups result in the formation of a chemical bond between the reactants or the chemical entities of each reactant.

Recognition group: Part of a tag and involved in the recognition of complementary recognitions groups of e.g. a complementary oligonucleotide. Preferred recognition groups are natural and non-natural nitrogeneous bases of a natural or non-natural nucleotide.

Recombine: A recombination process recombines two or more sequences by a process, the product of which is a sequence comprising sequences from each of the two or more sequences. When involving nucleotides, the recombination involves an exchange of nucleotide sequences between two or more nucleotide molecules at sites of identical nucleotide sequences, or at sites of nucleotide sequences that are not identical, in which case the recombination can occur randomly. One type of recombination among nucleotide sequences is referred to in the art as gene shuffling.

Residue: A molecule comprises a plurality of linked residues, wherein each residue comprises a functional group. A polymer comprises a sequence of covalently linked residues, wherein each residue comprises a functional group.

Ribose derivative: Ribose moiety forming part of a nucleoside capable of being enzymatically incorporated into a template or complementing template. Examples include e.g. derivatives distinguishing the ribose derivative from the riboses of natural ribonucleosides, including adenosine (A), guanosine (G), uridine (U) and cytidine (C). Further examples of ribose derivatives are described in e.g. US 5,786,461. The term covers derivatives of deoxyriboses, and analogously with the above-mentioned disclosure, derivatives in this case distinguishes the deoxyribose derivative from the deoxyriboses of natural deoxyribonucleosides, including deoxyadenosine (dA), deoxyguanosine (dG), deoxythymidine (dT) and deoxycytidine (dC).

Scaffold: Structural entity comprising one or more reactive groups, preferably more reactive groups, with which one or more reactants can react. A "scaffold" or "core scaffold" is a molecule that generally does not include chemical entities, as described herein, but may include internal chemical entities, such as atoms that are part of one of the central rings. A molecule comprises a scaffold and at least one chemical entity. Non-limiting examples of a scaffold include any cyclic or non-cyclic structure, such as, but not limited to, those disclosed herein. In some embodiments

of the invention, a scaffold is the portion of a molecule lacking one or more chemical entities. Compounds of the invention include those comprising a scaffold and one or more chemical entities. A scaffold preferably exhibits properties of desirable lead compounds, including, for example, a low molecular complexity (low number of hydrogen bond donors and acceptors, low number of rotatable bonds, and low molecular weight), and low hydrophobicity. Because a scaffold is small, one of ordinary skill in the art may further develop or elaborate the core into a lead or drug candidate by modifying the core to have desirable drug characteristics, including, for example, by meeting the Lipinski rule of five. Preferred core properties include lead-like properties and are known to those of ordinary skill in the art and are described in Teague, S. J., et al., Agnew. Chem. Int. Ed. 38:3743-3748, 1999; Oprea, T. I., et al., J. Chem. Inf. Comput. Sci. 41:1308-1315, 2001; and Hann, M. M. et al., J. Chem. Inf. Comput. Sci. 41:856-864, 2001. Thus, scaffolds are designed so that more complexity and weight can be added during development and building out of the molecule into a lead candidate, while maintaining the general properties.

Selectively cleavable linker: A selectively cleavable linkers are not cleavable under conditions wherein cleavable linkers is cleaved.

Specific recognition: The specific interaction of e.g. a nucleotide of a tag with preferably one predetermined nucleotide of an anti-tag constitutes a specific recognition. A specific recognition occurs when the affinity of a tag nucleotide recognition group for an anti-tag nucleotide recognition group results in the formation of predominantly only one type of corresponding binding partners. Simple mis-match incorporation does not exclude a specific recognition of corresponding binding partners.

Subunit: Monomer of a tag, such as e.g. a nucleotide.

Support: Solid or semi-solid member to which e.g. tags can be attached. Examples of supports includes planar surfaces including silicon wafers as well as beads.

Tag: Part of an identifier oligonucleotide. A tag is a string of consecutive nucleotides capable of identifying a particular reactant having reacted during the method of synthesising the molecule to which the identifier oligonucleotide is linked. A tag can be an element of an identifier, such as an identifier oligonucleotide, comprising one

or more recognition group(s) capable of recognising one or more predetermined, complementary recognition group(s). The recognition can be generated by and/or result in the formation of a covalent bond or a non-covalent bond between corresponding pairs of recognition groups capable of interacting with one another. The recognition groups can be nucleobases in a strand of consecutive nucleotides, such as an oligonucleotide.

Tag complementation: Contacting a tag with a predetermined, complementary tag (anti-tag) comprising recognition group(s) capable of recognising the recognition groups(s) of the tag. Hybridisation of complementary oligonucleotides (anti-tags) represents one example of a tag complementation. The complementation occurs when a tag is brought into reactive contact with a predetermined, complementary tag capable of recognising the recognition group(s) of the tag. When the tag and the complementary tag (anti-tag) both comprises nucleotides, predetermined sets of nucleotides are capable of complementing each other by means of hydrogen bonds formed between the base moieties of the tags and the anti-tags capable of hybridising thereto.

Target molecule: Any compound of interest for which a templated molecule in the form of a ligand is desired. A target molecule can be a protein, fusion protein, peptide, enzyme, nucleic acid, nucleic acid binding protein, carbohydrate, polysaccharide, glycoprotein, hormone, receptor, receptor ligand, cell membrane component, antigen, antibody, virus, virus component, substrate, metabolite, transition state analog, cofactor, inhibitor, drug, controlled substance, dye, nutrient, growth factor, toxin, lipid, glycolipid, etc., without limitation.

Variant: Molecule exhibiting a certain degree of identity or homology - either physically or functionally - to a predetermined molecule.
The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene ($-CH_2-$) radical.

Where the term "alkyl" is used, either alone or within other terms such as "haloalkyl" and "alkylsulfonyl", it embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. Preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms, such

as lower alkyl radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl and the like. Branched chain isomers of straight chain alkyl groups, include, but are not limited to, the following which are provided by way of example: $-CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-CH(CH_2CH_3)_2$, $-C(CH_3)_3$, $-C(CH_2CH_3)_3$, $-CH_2CH(CH_3)_2$, $-CH_2CH(CH_3)(CH_2CH_3)$, $-CH_2CH(CH_2CH_3)_2$, $-CH_2C(CH_3)_3$, $-CH_2C(CH_2CH_3)_3$, $-CH(CH_3)CH(CH_3)(CH_2CH_3)$, $-CH_2CH_2CH(CH_3)_2$, $-CH_2CH_2CH(CH_3)(CH_2CH_3)$, $-CH_2CH_2CH(CH_2CH_3)_2$, $-CH_2CH_2C(CH_3)_3$, $-CH_2CH_2C(CH_2CH_3)_3$, $-CH(CH_3)CH_2CH(CH_3)_2$, $-CH(CH_3)CH(CH_3)CH(CH_3)CH(CH_3)_2$, $-CH(CH_2CH_3)CH(CH_3)CH(CH_3)(CH_2CH_3)$, and others. When substituted, the “alkyl” or “lower alkyl” can comprise one or more radicals selected from the group of radicals consisting of hydroxy, primary amine, carboxy, acid chloride, sulfonyl chloride, sulphonate, nitro, cyano, isothiocyanate, halogen, phosphonyl, sulphonyl, sulfamyl, carbonyl, and thiolyl.

The term "alkenyl" embraces linear or branched radicals having at least one carbon-carbon double bond of two to about twenty carbon atoms, such as from two to about twelve carbon atoms, for example from two to about eight carbon atoms. Preferred alkyl radicals are "lower alkenyl" radicals having two to about six carbon atoms. Examples of such radicals include ethenyl, n-propenyl, butenyl, and the like. When substituted, the “alkenyl” or “lower alkenyl” can comprise one or more radicals selected from the group of radicals consisting of hydroxy, primary amine, carboxy, acid chloride, sulfonyl chloride, sulphonate, nitro, cyano, isothiocyanate, halogen, phosphonyl, sulphonyl, sulfamyl, carbonyl, and thiolyl.

The term "halo" means halogens such as fluorine, chlorine, bromine or iodine atoms. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" preferably embraces radicals having 1-6 carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl

and dichloropropyl. The “haloalkyl” or “lower haloalkyl” can optionally be further substituted. When further substituted, the “haloalkyl” or “lower haloalkyl” can further comprise one or more radicals selected from the group of radicals consisting of hydroxy, primary amine, carboxy, acid chloride, sulfonyl chloride, sulphonate, nitro, cyano, isothiocyanate, phosphonyl, sulphonyl, sulfamyl, carbonyl, and thiolyl.

The term "hydroxyalkyl" embraces linear or branched alkyl radicals having from one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. Hydroxyalkyl radicals can be "lower hydroxyalkyl" radicals preferably having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl. The “hydroxyalkyl” or “lower hydroxyalkyl” can optionally be further substituted. When further substituted, the “hydroxyalkyl” or “lower hydroxyalkyl” can further comprise one or more radicals selected from the group of radicals consisting of primary amine, carboxy, acid chloride, sulfonyl chloride, sulphonate, nitro, cyano, isothiocyanate, halogen, phosphonyl, sulphonyl, sulfamyl, carbonyl, and thiolyl.

The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy radical. Alkoxy radicals can be "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and tert-butoxy. The term "alkoxyalkyl" also embraces alkyl radicals having two or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. Alkoxyalkyl radicals can be "lower alkoxyalkyl" radicals having one to six carbon atoms and one or two alkoxy radicals. Examples of such radicals include methoxymethyl, methoxyethyl, ethoxyethyl, methoxybutyl and metoxypropyl. The alkyl in said “alkoxyalkyl” can be substituted with one or more of hydroxy, primary amine, carboxy, acid chloride, sulfonyl chloride, sulphonate, nitro, cyano, isothiocyanate, halogen, phosphonyl, sulphonyl, sulfamyl, carbonyl, and thiolyl. When e.g. the above "alkoxyl" or "alkoxyalkyl" radicals are substituted with one or more halo atoms, such as fluoro, chloro or bromo, "haloalkoxy" or "haloalkoxyalkyl" radicals are provided. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy.

The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. When substituted, “aryl” can comprise one or more radicals selected from the group of radicals consisting of hydroxy, primary amine, carboxy, acid chloride, sulfonyl chloride, sulphonate, nitro, cyano, isothiocyanate, halogen, phosphonyl, sulphonyl, sulfamyl, carbonyl, and thiolyl. Examples of “aryl” include aromatic radicals such as phenyl, pentafluorphenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl.

The term "heterocyclic" embraces saturated, partially saturated and unsaturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. When substituted, “heterocyclic” can comprise one or more radicals selected from the group of radicals consisting of hydroxy, primary amine, carboxy, acid chloride, sulfonyl chloride, sulphonate, nitro, cyano, isothiocyanate, halogen, phosphonyl, sulphonyl, sulfamyl, carbonyl, and thiolyl. Examples of saturated heterocyclic radicals include e.g. saturated 3 to 6-membered heteromonocylic group containing 1 to 4 nitrogen atoms [e.g. pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. morpholinyl, etc.]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g. thiazolidinyl, etc.]. Examples of partially saturated heterocyclic radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole.

The term "heteroaryl" embraces unsaturated heterocyclic radicals. When substituted, “heteroaryl” can comprise one or more radicals selected from the group of radicals consisting of hydroxy, primary amine, secondary amine, carboxy, acid chloride, sulfonyl chloride, sulphonate, nitro, cyano, isothiocyanate, halogen, phosphonyl, sulphonyl, sulfamyl, carbonyl, and thiolyl. Examples of unsaturated heterocyclic radicals, also termed "heteroaryl" radicals, include e.g. unsaturated 5 to 6 membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.] tetrazolyl [e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.], etc.; unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl,

tetrazolopyridazinyl [e.g., tetrazolo [1,5-b]pyridazinyl, etc.], etc.; unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, 2-furyl, 3-furyl, etc.; unsaturated 5 to 6-membered heteromonocyclic group containing a sulfur atom, for example, 2-thienyl, 3-thienyl, etc.; unsaturated 5- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.] etc.; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl, etc.]; unsaturated 5 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.] etc.; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl, etc.] and the like. The term “heteroaryl” or “unsaturated heterocyclic radical” also embraces radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. Said "heterocyclic group" can be substituted with one or more radicals selected from the group of radicals consisting of hydroxy, primary amine, carboxy, acid chloride, sulfonyl chloride, sulphonate, nitro, cyano, isothiocyanate, halogen, phosphonyl, sulphonyl, sulfamyl, carbonyl, and thiolyl, said substitution generating a substituted “heteroaryl”, optionally a substituted “heteroaryl” fused with an “aryl” radical which can be substituted or un-substituted. When substituted, the “aryl” is substituted as described herein above. Preferred heterocyclic radicals include five to ten membered fused or unfused radicals. More preferred examples or heteroaryl radicals include benzofuryl, 2,3-dihydrobenzofuryl, benzotrienyl, indolyl, dihydroindolyl, chromanyl, benzopyran, thiochromanyl, benzothiopyran, benzodioxolyl, benzodioxanyl, pyridyl, thienyl, thiazolyl, oxazolyl, furyl, and pyrazinyl.

The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals $-SO_2-$.

"Alkylsulfonyl" embraces alkyl radicals attached to a sulfonyl radical, where alkyl can be substituted is defined as above. Alkylsulfonyl radicals can be "lower alkylsulfonyl" radicals having one to six carbon atoms. Examples of such lower alkylsulfonyl radicals include methylsulfonyl, ethylsulfonyl and propylsulfonyl.

The term "arylsulfonyl" embraces aryl radicals as defined above, including substituted aryl radicals, attached to a sulfonyl radical. Examples of such radicals include phenylsulfonyl.

The terms "sulfamyl," "aminosulfonyl" and "sulfonamidyl," whether alone or used with terms such as "N-alkylaminosulfonyl", "N-arylaminosulfonyl", "N,N-dialkylaminosulfonyl" and "N-alkyl-N-arylaminosulfonyl", denotes a sulfonyl radical substituted with an amine radical, forming a sulfonamide ($-SO_2NH_2$).

The terms "N-alkylaminosulfonyl" and "N,N-dialkylaminosulfonyl" denote sulfamyl radicals substituted respectively, with one alkyl radical, or two alkyl radicals, optionally substituted alkyl radicals as described herein above. Akylaminosulfonyl radicals can be "lower alkylaminosulfonyl" radicals having one to six carbon atoms. Examples of such lower alkylaminosulfonyl radicals include N-methylaminosulfonyl, N-ethylaminosulfonyl and N-methyl-N-ethylaminosulfonyl.

The terms "N-arylaminosulfonyl" and "N-alkyl-N-arylaminosulfonyl" denote sulfamyl radicals substituted, respectively, with one aryl radical, or one alkyl and one aryl radical, optionally substituted aryl and/or alkyl radicals as described herein above. N-alkyl-N-arylaminosulfonyl radicals can be "lower N-alkyl-N-arylsulfonyl" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower N-alkyl-N-aryl aminosulfonyl radicals include N-methyl-phenylaminosulfonyl and N-ethyl-phenylaminosulfonyl.

The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes $-CO_2H$.

The term "carboxyalkyl" or "alkanoyl" embraces radicals having a carboxy radical as defined above, attached to an alkyl radical as described herein above. When substituted, the “alkyl” or “lower alkyl” can comprise one or more radicals selected from the group of radicals consisting of hydroxy, primary amine, carboxy, acid chloride, sulfonyl chloride, sulphonate, nitro, cyano, isothiocyanate, halogen, phosphonyl, sulphonyl, sulfamyl, carbonyl, and thiolyl. Examples of “carboxyalkyl” radicals include formyl, acetyl, propionyl (propanoyl), butanoyl (butyryl), isobutanoyl (isobutyryl), valeryl (pentanoyl), isovaleryl, pivaloyl, hexanoyl or the like.

The term "carbonyl", whether used alone or with other terms, such as "alkylcarbonyl", denotes -(C=O)-.

The term "alkylcarbonyl" embraces radicals having a carbonyl radical substituted with an alkyl radical. Alkylcarbonyl radicals can be "lower alkylcarbonyl" radicals having from one to six carbon atoms. Examples of such radicals include methylcarbonyl and ethylcarbonyl. When substituted, the “alkyl” or “lower alkyl” of the “alkylcarbonyl” can comprise one or more radicals selected from the group of radicals consisting of hydroxy, primary amine, carboxy, acid chloride, sulfonyl chloride, sulphonate, nitro, cyano, isothiocyanate, halogen, phosphonyl, sulphonyl, sulfamyl, and thiolyl.

The term "alkylcarbonylalkyl", denotes an alkyl radical substituted with an "alkylcarbonyl" radical as described herein above. Both the alkyl and the alkylcarbonyl can be substituted as described herein above.

The term "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl radical. "Lower alkoxycarbonyl" embraces alkoxy radicals preferably having from one to six carbon atoms. Examples of "lower alkoxycarbonyl" ester radicals include substituted or unsubstituted methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and hexyloxycarbonyl.

The term "alkoxycarbonylalkyl" embraces radicals having "alkoxycarbonyl", as defined above substituted to an optionally substituted alkyl radical. Alkoxycarbonylalkyl radicals can be "lower alkoxycarbonylalkyl" having lower alkoxycarbonyl radicals as defined above attached to one to six carbon atoms. Examples of such lower alkoxycarbonylalkyl radicals include methoxycarbonylmethyl, tert-butoxycarbonylethyl, and methoxycarbonylethyl.

The term "aminocarbonyl" when used by itself or with other terms such as "aminocarbonylalkyl", "N-alkylaminocarbonyl", "N-arylaminocarbonyl, "N,N-dialkylaminocarbonyl", "N-alkyl-N-arylaminocarbonyl", "N-alkyl-N-hydroxyaminocarbonyl" and "N-alkyl-N-hydroxyaminocarbonylalkyl", denotes an amide group of the formula --C(=O)NH_2.

The terms "N-alkylaminocarbonyl" and "N,N-dialkylaminocarbonyl" denote aminocarbonyl radicals which have been substituted with one alkyl radical and with two alkyl radicals, respectively. The alkyl radicals can be substituted as described herein above. "Lower alkylaminocarbonyl" comprises lower alkyl radicals as described above attached to an aminocarbonyl radical.

The terms "N-arylaminocarbonyl" and "N-alkyl-N-arylaminocarbonyl" denote aminocarbonyl radicals substituted, respectively, with one aryl radical, or one alkyl and one aryl radical, wherein such radicals can be substituted as described herein above.

The term "aminocarbonylalkyl" embraces optionally substituted alkyl radicals substituted with aminocarbonyl radicals.

The term "N-cycloalkylaminocarbonyl" denotes aminocarbonyl radicals which have been substituted with at least one optionally substituted cycloalkyl radical. "Lower cycloalkylaminocarbonyl" comprises lower cycloalkyl radicals of three to seven carbon atoms, attached to an aminocarbonyl radical.

The term "aminoalkyl" embraces alkyl radicals substituted with one or more amino radicals. The alkyl radicals can be further substituted by one or more radicals selected from the group of radicals consisting of hydroxy, carboxy, acid chloride, sulfonyl chloride, sulphonate, nitro, cyano, isothiocyanate, halogen, phosphonyl, sulphonyl, sulfamyl, carbonyl, and thiolyl.

The term "alkylaminoalkyl" embraces aminoalkyl radicals having the nitrogen atom substituted with an optionally substituted alkyl radical.

The term "amidino" denotes an $-C(=NH)-NH_2$ radical.

The term "cyanoamidino" denotes an $-C(=N-CN)-NH_2$ radical.

The term "heterocyclicalkyl" embraces heterocyclic-substituted alkyl radicals. The alkyl radicals can themselves be substituted by one or more radicals selected from the group of radicals consisting of hydroxy, primary amino, carboxy, acid chloride,

sulfonyl chloride, sulphonate, nitro, cyano, isothiocyanate, halogen, phosphonyl, sulphonyl, sulfamyl, carbonyl, and thiolyl. Heterocyclicalkyl radicals can be "lower heterocyclicalkyl" radicals preferably having from one to six carbon atoms and a heterocyclic radical. Examples include such radicals as pyrrolidinylmethyl, pyridylmethyl and thienylmethyl.

The term "aralkyl" embraces aryl-substituted alkyl radicals. The alkyl radicals can themselves be substituted by one or more radicals selected from the group of radicals consisting of hydroxy, primary amino, carboxy, acid chloride, sulfonyl chloride, sulphonate, nitro, cyano, isothiocyanate, halogen, phosphonyl, sulphonyl, sulfamyl, carbonyl, and thiolyl. Aralkyl radicals can be "lower aralkyl" radicals having aryl radicals attached to alkyl radicals having from one to six carbon atoms. Examples of such radicals include benzyl, diphenylmethyl, triphenylmethyl, phenylethyl and diphenylethyl. The aryl in said aralkyl may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy. The terms benzyl and phenylmethyl are interchangeable.

The term "cycloalkyl" embraces radicals having three to ten carbon atoms. Cycloalkyl radicals can be "lower cycloalkyl" radicals having three to seven carbon atoms. Examples include radicals such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. The “cycloalkyl” can optionally be substituted by one or more radicals selected from the group of radicals consisting of hydroxy, primary amine, carboxy, acid chloride, sulfonyl chloride, sulphonate, nitro, cyano, isothiocyanate, halogen, phosphonyl, sulphonyl, sulfamyl, carbonyl, and thiolyl.

The term "cycloalkenyl" embraces unsaturated cyclic radicals having three to ten carbon atoms. The “cycloalkenyl” can optionally be substituted by one or more radicals selected from the group of radicals consisting of hydroxy, primary amine, carboxy, acid chloride, sulfonyl chloride, sulphonate, nitro, cyano, isothiocyanate, halogen, phosphonyl, sulphonyl, sulfamyl, carbonyl, and thiolyl. Examples include cyclobutenyl, cyclopentenyl, cyclohexenyl and cycloheptenyl, which can optionally be substituted as described above.

The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. An example of

"alkylthio" is methylthio, (CH_3-S-). The alkyl radical can be substituted as described herein above.

The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent -S(=O)- atom. The alkyl radical can be substituted as described herein above.

The term "aminoalkyl" embraces alkyl radicals substituted with amino radicals. The alkyl radicals can be further substituted by one or more radicals selected from the group of radicals consisting of hydroxy, carboxy, acid chloride, sulfonyl chloride, sulphonate, nitro, cyano, isothiocyanate, halogen, phosphonyl, sulphonyl, sulfamyl, carbonyl, and thiolyl. Aminoalkyl radicals can be "lower aminoalkyl" having from one to six carbon atoms. Examples include aminomethyl, aminoethyl and aminobutyl which can optionally be further substituted as described above.

The term "alkylaminoalkyl" embraces aminoalkyl radicals having the nitrogen atom substituted with at least one alkyl radical. Alkylaminoalkyl radicals can be "lower alkylaminoalkyl" having one to six carbon atoms attached to a lower aminoalkyl radical as described above. The alkyl radical can be substituted as described herein above.

The terms "N-alkylamino" and "N,N-dialkylamino" denote amino groups which have been substituted with one alkyl radical and with two alkyl radicals, respectively. The alkyl radical can be substituted as described herein above. Alkylamino radicals can be "lower alkylamino" radicals having one or two alkyl radicals of one to six carbon atoms, attached to a nitrogen atom. Suitable "alkylamino" may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino or the like.

The term "arylamino" denotes amino groups which have been substituted with one or two aryl radicals, such as N-phenylamino. The "arylamino" radicals may be further substituted on the aryl ring portion of the radical. Substitutions can include one or more of hydroxy, amino, carboxy, acid chloride, sulfonyl chloride, sulphonate, nitro, cyano, isothiocyanate, halogen, phosphonyl, sulphonyl, sulfamyl, carbonyl, and thiolyl.

The term "aralkylamino" denotes amino groups which have been substituted with one or two aralkyl radicals, such as N-benzylamino. The "aralkylamino" radicals may be further substituted on the aryl ring portion of the radical. Substitutions can include one or more of hydroxy, amino, carboxy, acid chloride, sulfonyl chloride, sulphonate, nitro, cyano, isothiocyanate, halogen, phosphonyl, sulphonyl, sulfamyl, carbonyl, and thiolyl.

The terms "N-alkyl-N-arylamino" and "N-aralkyl-N-alkylamino" denote amino groups which have been substituted with one aralkyl and one alkyl radical, or one aryl and one alkyl radical, respectively, to an amino group. The aralkyl and/or alkyl and/or aryl radicals can be substituted as described herein above.

The terms "N-arylaminoalkyl" and "N-aralkylaminoalkyl" denote amino groups which have been substituted with one aryl radicals or one aralkyl radical, respectively, and having the amino group attached to an alkyl radical. The aralkyl and/or alkyl and/or aryl radicals can be substituted as described herein above. Arylaminoalkyl radicals can be "lower arylaminoalkyl" having the arylamino radical attached to one to six carbon atoms. Examples of such radicals include N-phenylaminomethyl and N-phenyl-N-methylaminomethyl.

The terms "N-alkyl-N-arylaminoalkyl", and "N-aralkyl-N-alkylaminoalkyl" denote N-alkyl-N-arylamino and N-alkyl-N-aralkylamino groups, respectively, and having the amino group attached to alkyl radicals which can be substituted as described herein above.

The term "acyl", whether used alone, or within a term such as "acylamino", denotes a radical provided by the residue after removal of hydroxyl from an organic acid.

The term "acylamino" embraces an amino radical substituted with an acyl group. An examples of an "acylamino" radical is acetylamino or acetamido ($CH_3C(=O)$-NH-) where the amine may be further substituted with alkyl, aryl or aralkyl, wherein said alkyl, aryl or aralkyl can be substituted as described herein above.

The term "arylthio" embraces aryl radicals of six to ten carbon atoms, attached to a divalent sulfur atom. The aryl can be substituted as described herein above. An example of "arylthio" is phenylthio.

The term "aralkylthio" embraces aralkyl radicals as described above, attached to a divalent sulfur atom. The aralkyl radicals can be further substituted as described herein above.An example of "aralkylthio" is benzylthio.

The term "aryloxy" embraces aryl radicals, as defined above, attached to an oxygen atom. The aryl can be substituted as described herein above. Examples of such radicals include phenoxy.

The term "aralkoxy" embraces oxy-containing aralkyl radicals attached through an oxygen atom to other radicals. The aralkyl can be substituted as described herein above.Aralkoxy radicals can be “lower aralkoxy" radicals having phenyl radicals attached to lower alkoxy radical as described above.

The term "haloaralkyl" embraces aryl radicals as defined above attached to haloalkyl radicals. The aryl can be further substituted as described herein above.

The term "carboxyhaloalkyl" embraces carboxyalkyl radicals as defined above having halo radicals attached to the alkyl portion. The alkyl portion can be further substituted as described herein above.

The term "alkoxycarbonylhaloalkyl" embraces alkoxycarbonyl radicals as defined above substituted on a haloalkyl radical. The haloalkyl radical can be further substituted by one or more of hydroxy, amino, carboxy, acid chloride, sulfonyl chloride, sulphonate, nitro, cyano, isothiocyanate, phosphonyl, sulphonyl, sulfamyl, carbonyl, and thiolyl.

The term "aminocarbonylhaloalkyl" embraces aminocarbonyl radicals as defined above substituted on an optionally substituted haloalkyl radical wherein the alkyl is substituted by one or more of hydroxy, amino, carboxy, acid chloride, sulfonyl chloride, sulphonate, nitro, cyano, isothiocyanate, phosphonyl, sulphonyl, sulfamyl, carbonyl, and thiolyl.

The term "alkylaminocarbonylhaloalkyl" embraces alkylaminocarbonyl radicals as defined above substituted on an optionally substituted haloalkyl radical as described above.

The term "alkoxycarbonylcyanoalkenyl" embraces alkoxycarbonyl radicals as defined above, and a cyano radical, both substituted on an optionally substituted alkenyl radical.

The term "carboxyalkylaminocarbonyl" embraces aminocarbonyl radicals substituted with carboxyalkyl radicals, as defined above. The carboxyalkyl can be further substituted. Substitutions can include one or more of hydroxy, amino, acid chloride, sulfonyl chloride, sulphonate, nitro, cyano, isothiocyanate, halogen, phosphonyl, sulphonyl, sulfamyl, carbonyl, and thiolyl.

The term "aralkoxycarbonylalkylaminocarbonyl" embraces aminocarbonyl radicals substituted with aryl-substituted alkoxycarbonyl radicals, as defined above.

The term "cycloalkylalkyl" embraces cycloalkyl radicals having three to ten carbon atoms attached to an alkyl radical, as defined above. Cycloalkylalkyl radicals can be "lower cycloalkylalkyl" radicals having cycloalkyl radicals attached to lower alkyl radicals as defined above. Examples include radicals such as cyclopropylmethyl, cyclobutylmethyl, and cyclohexylethyl.

The term "aralkenyl" embraces optionally substituted aryl radicals attached to alkenyl radicals having two to ten carbon atoms, such as phenylbutenyl, and phenylethenyl or styryl. When substituted the aryl can be substituted with one or more of hydroxy, amino, carboxy, acid chloride, sulfonyl chloride, sulphonate, nitro, cyano, isothiocyanate, halogen, phosphonyl, sulphonyl, sulfamyl, carbonyl, and thiolyl.

Brief disclosure of the Figures

Figure 1. A tag addition process employing linkage of top strand tags only. (a) The initial binfunctional complex. (b-e) Addition of tags A to D. (f) The top strand containing tags A to D. (h) The individual anti-tags Ax to Dx. The polarity of overhangs is such that B, C, and D tags contact their cognant anti-tag and the anti-tag cognate to the following tag, e.g. a B-tag contacts an anti-B-tag and an anti-C-tag.

Figure 2. One possible type of tag layout. (a) The initial bifunctional complex containing a chemical reaction site, a linker moiety, and a tag region (linker tag). (b) Tags A, B, C, and D containing a tag region and an overhang region. (c) The anti-A-tag containing an anti-linker tag region and an anti-A-tag region. (d) Anti-tags Ax, Bx, Cx, and Dx containing an anti-overhang region and an anti-tag region.

Figure 3. A tag addition process employing linkage of top strand tags only and using non-abutting anti-tags, i.e., the anti-tags are separated from each other. (a) The initial binfunctional complex. (b-e) Addition of tags A to D. (f) The top strand containing tags A to D. (h) The individual anti-tags Ax to Dx. The polarity of overhangs is such that B, C, and D tags contact their cognant anti-tag and the anti-tag cognate to the following tag, e.g. a B-tag contacts an anti-B-tag and an anti-C-tag.

Figure 4. Different possible designs of the initial bifunctional complex. (a) a single chemical reaction site is attached to a single linker tag via a non-branched linker. (b) A number (n) of chemical reaction sites are attached to a single linker tag via a branched linker. (c) A single chemical reaction site is attached to a number (n) of linker tags via a branched linker. (d) A number (n) of chemical reaction sites are attached to a number (n) of linker tags via a branched linker.

Figure 5. A tag addition process employing linkage of top strand tags only. (a) The initial binfunctional complex. (b-e) Addition of tags A to D. (f) The top strand containing tags A to D. (h) The individual anti-tags Ax to Dx. The polarity of overhangs is such that B, C, and D tags contact their cognant anti-tag and the anti-tag cognate to the previous tag (compare with figure 1), e.g. a B-tag contacts an anti-B-tag and an anti-A-tag.

Figure 6. A tag addition process employing linkage of top strand tags only and removal of anti-tags after each cycle of tag addition. (a) The initial binfunctional complex. (b-e) Addition of tags A to D. (f) The top strand containing tags A to D. The polarity of overhangs is such that B, C, and D tags contact their cognant anti-tag and the anti-tag cognate to the following tag, e.g. a B-tag contacts an anti-B-tag and an anti-C-tag.

Figure 7. The primer extension process. (a) An extension primer is annealed to the single tag strand containing tags. (b) Extension of the primer results in a double-stranded tag.

Figure 8. Examples of chemical reactions using an amine as a chemical reaction site.

Figure 9. Examples of chemical reactions using an acid as a chemical reaction site.

Figure 10. Examples of chemical reactions using an aldehyde or a ketone as a chemical reaction site.

Figure 11. Examples of chemical reactions using Wittig or Horner-Wadsworth-Emmons reaction substrates.

Figure 12. Examples of chemical reactions generating a dinucleophile.

Figure 13. Examples of monofunctional versus multifunctional reactions. (a) monofunctional reaction. (b) bifunctional reaction generating a heterocyclic molecule.

Figure 14. Examples of bifunctional electrophiles.

Figure 15. Examples of chemical reactions of 1,2-dielectrophiles.

Figure 16. Examples of chemical reactions of 1,3-dielectrophiles.

Figure 17. Examples of transformations of building blocks (reactants) into heterocycles.

Figure 18. Examples of heterocyclic structures generated using bifunctional reactions.

Figure 19. Examples of chemical reactions generating bicyclic structures (I).

Figure 20. Examples of chemical reactions generating bicyclic structures (II).

Figure 21. Examples of chemical reaction matrix illustrating how building blocks (reactants) (rows and columns) can be combined to form cyclic structures.

Figures 22-23. The figures serve to illustrate the formation of molecules / product structures formed by the process.
The figures represent examples, which are not meant to limit the scope of the invention. In Figure 22, the following steps are illustrated:
Step i.: E.g. enzymatical ligation of one oligonucleotide tag to the display oligonucleotide.
Step ii.: E.g. Reacting one reactant with the chemical reaction site in the formation of one or more covalent bonds.
Step iii.: Reactive groups may optionally be transformed into other reactive groups, such as for example but not limited to the deprotection of one reactive group into another reactive group, for example deprotection of a amino protection group, whereby a reactive amine will be formed, for example deprotection of an ester, whereby a reactive carboxylic acid will be formed, for example oxidation of a 1,2-diol using periodate, whereby a reactive aldehyde will be formed.
Step iv.: Optionally repeat step iii., optionally repeat step i. and ii. Optionally, conduct further repetition of step iv. and other steps in accordance with and as described and claimed by this invention.

Figure 23. Reactants may be reacted prior to (step ii) reactions with the chemical reaction site (step iii).

Figure 24 The figure serves to illustrate example reactants comprising one or more chemical entities and one or more reactive groups. The invention is not limited to the use of the reactants shown. Reactants may furthermore be protected by use of one or more protection groups.
Reactants within a group comprising one or more identical reactive groups may comprise different chemical entities, which may be focused around specific core structures or which may be diverse (different) or the group may comprise a combination of focused and diverse chemical entities.
Reactants in different groups of reactive groups may be focused around specific core structures or may be diverse (different) or the groups may comprise a combination of focused and diverse chemical entities.

Figures 25-36. Circles with a number inside, denotes reactants. The figures serve to illustrate various product structures formed by the use of reactants in various ways. Emphasized (thick) lines denotes a product structure formed by the reaction of one or more reactive groups on one or more reactants and a product structure formed by the reaction of one or more reactive groups on one or more reactants and one or more chemical reaction sites. The product structure does not need to comprise atoms (direct covalent linkage of two reactants). The product structure may also comprise one or more bonds and one or more atoms. The product structure may be cyclic or linear or branched or combinations thereof. The product structure may for example also comprise product structure examples as described elsewhere by this invention. Product structures represented by thick lines may be the same or different.

Figures 37-50. In some figures a pyrimidine product structure is used as an example for a heteroaromatic chemical structure e.g. an azine, such as for example a pyridine, a pyrimidine, a pyrazine, a pyridazine, a purine and for example benzo and azolo variants thereof. Azine product structure examples are also exemplified elsewhere in this invention.

Definitions used:
CRS: Chemical reactive site
Chemical entities are denoted / illustrated by R groups, which may have numbers such as R1, R2, R3, R4, R5, R6, R7, R8, R9, R10. Chemical entities may also be shown as a circle with an R group inside. Such circles may optionally represent a cyclic structure, e.g. R1 may be a cyclic structure such as e.g. a cyclic diamino acid, for example but not limited to the product following the use of piperidine 2-carboxylic acid as reactant, whereby two amino groups may react with similar or different electrophiles, such as for example reaction with aldehydes under reductive amination conditions to form an alkylated amine, for example reaction with a sulfonyl chloride to form sulfonamides, for example acylation by reaction with carboxylic acids under for example EDC/NHS or DMTMM coupling conditions to form carboxamides, for example reaction with haloazines to form aminoazines, and the carboxylic acid of the diaminoacid may undergo an acylation reaction to form an amide. Although illustrated by circles, the back bone / core / scaffolded structure

may in fact be either cyclic or non-cyclic, including branched, linear, cyclic structures or a combination thereof.

Amino groups may be primary amines, secondary amines, tertiary amines. Amide groups may be primary, secondary, tertiary amides. When the circle represents a cyclic structure, amines may be endocyclic or exocyclic.

Het: means a heterocyclic product structure for example an azine, an azole, a purine, and other heterocyclic systems as defined elsewhere in the invention. Aromatic rings with an N inside the ring are by definition equivalent to Het. Pyrimidine structures are also equivalent to the definition of Het and the pyrimidine structure is only used to illustrate the example and not to limit the scope of this invention.

Figures 37-39. The figure describes various example product structures formed by use of at least one reactant. In some examples reactants comprising further reactive groups may react with further reactants to form linear, branched, cyclic, macrocyclic structures or a combination thereof or undergo intramolecular cyclization through the reaction with further reactive groups on R1, including reactive groups not shown but comprised by R1.

Figures 40-50. The figure describes various product structures formed by use of 1-5 reactants, for example one reactant, for example 2 reactants, for example 3 reactants, for example 4 reactants, for example 5 reactants. In some examples reactants comprising further reactive groups may react with further reactants to form linear, branched, cyclic or macrocyclic structures or undergo intramolecular cyclization through the reaction with further reactive groups on Rn-groups, including reactive groups not shown but comprised by Rn-groups (where n is an integer). The invention may also use more than five reactants, such as six reactants, for example seven reactants, for example eight reactants, for example nine reactants, for example ten reactants. In another embodiment, 11-20 reactants are used, such as 11-15 reactants, for example 16-20 reactants.

Figure 51. The figure illustrates a member of a tetramer library consisting of bifunctional molecules each comprising 4 DNA codon elements (tags) covalently linked to the cognate chemical fragments. The overall structure of the bifunctional molecules is shown. Each 20 nt/bp codon is spaced by a 10 nt fixed region and the tags A-D is flanked by fixed sequences useful for amplification by PCR.

Figure 52. Panel A illustrates a single stranded identifier oligonucleotide linked to a reactive entity (chemical reaction site). Panel B illustrates iterative steps of subtraction of specifically formed duplexes between the anti-tags supplied and the corresponding identifier codon sequences.

Figure 53. Illustration of a simple quadruple amino-DNA tag enabling synthesis and display of the same encoded molecule attached to a single encoding tag. It may be desirable to include spacing groups such as polyethylene glycol (PEG) units at any point in the synthesis process (chosen by the experimenter) for improved synthesis and display of the synthetic molecule.

Figure 54. The figure depicts a scheme for the addition, by hybridization, of a helper molecule covalently linked to a DNA sequence complementary to the region of DNA of the bifunctional library molecule that is proximal to the displayed molecule. Hybridization of a second primer followed by polymerase extention and ligation will produce dsDNA displaying both the encoded library molecule and the helper molecule

Figure 55. In a split and mix library generation procedure n chemical reactions are conducted producing n chemical fragments linked to N different tags producing intermediates with a common structure.

Figure 56. The figure illustrates an alternative method for the purification of the control mimics in the library is to include a selective cleavable linker connecting a handle for purification and the reactive chemical unit.

Figure 57. The figure illustrates an alternative method for the purification of the control mimics in a library. A selectively cleavable linker connecting a handle for purification and the reactive chemical unit is included. The reactive unit (site) is any suitable reactive groups, for example, but not limited to, an amino, thiol, carboxylic-acid or aldehyd-group. The oligonucleotide moiety is optional but provides an excellent handle for molecular weight analysis using MS. The cleavable linker (optionally) is selectively cleavable by any means such as e.g. by enzymatic, chemical or photocleavable methods. The purification (optional) may be any unit capable of being selectively recovered.

Figure 58. The figure illustrates exemplary reaction chemistries applicable to the present invention.

Disclosure of the Invention

The methods and products pertaining to the present invention are further disclosed in more detail herein below. The examples demonstrating the utility of the present invention should not be construed as a limitation of the scope of protection conferred by the patent claims.

Nucleotides

A tag comprises recognition units, i.e. units which can be recognized by recognition groups. The recognition units making up a tag possesses information so as to identify a reactant having participated in the synthesis of the molecule. Generally, it is preferred that the tag comprises or consists of a sequence of nucleotides.

Individual tags can be distinguished from each other e.g. by a difference in only a single nucleotide position, such as a deletion, an insertion or a mutation. However, to facilitate a subsequent decoding process it is in general desirable to have two or more differences in the nucleotide sequence of any two tags.

In the event two or more reactants are reacted with the chemical reactive site, the tags of the identifier oligonucleotide can be separated by a constant region or a binding region. One function of the binding region can be to establish a platform at which an enzyme, such as polymerase or ligase can recognise as a substrate. Depending on the molecule formed, the identifier oligonucleotide can comprise further tags, such as 2, 3, 4, 5, or more tags. Each of the further tags can be separated by a suitable binding region.

All or at least a majority of the tags of the identifier oligonucleotide can be separated from a neighbouring tag by a binding sequence. The binding region may have any suitable number of nucleotides, e.g. 1 to 20. The binding region, if present, may serve various purposes besides serving as a substrate for an enzyme. In one setup of the invention, the binding region identifies the position of the tag. Usually, the

binding region either upstream or downstream of a tag comprises information which allows determination of the position of the tag. In another setup, the binding regions have alternating sequences, allowing for addition of reactants from two pools in the formation of the library. Moreover, the binding region may adjust the annealing temperature to a desired level.

A binding region with high affinity can be provided by one or more nucleobases forming three hydrogen bonds to a cognate nucleobase. Examples of nucleobases having this property are guanine and cytosine. Alternatively, or in addition, the binding region can be subjected to backbone modification. Several backbone modifications provides for higher affinity, such as 2'-O-methyl substitution of the ribose moiety, peptide nucleic acids (PNA), and 2'-4' O-methylene cyclisation of the ribose moiety, also referred to as LNA (Locked Nucleic Acid).

The identifier oligonucleotide can optionally further comprise flanking regions around the tag. The flanking region can encompass a signal group, such as a flourophor or a radio active group to allow for detection of the presence or absence of a complex or the flanking region may comprise a label that can be detected, such as biotin. When the identifier comprises a biotin moiety, the identifier may easily be recovered.

The flanking regions can also serve as priming sites for amplification reactions, such as PCR. Usually, the last cycle in the formation of the bifunctional complex includes the incorporation of a priming site. A region of the bifunctional complex close to the molecule, such as a nucleic acid sequence between the molecule and the tag coding for the scaffold molecule, is usually used for another priming site, thereby allowing for PCR amplification of the coding region of the bifunctional complex.

Apart from a combination of the nucleotides coding for the identity of the reactant, a tag may comprise further nucleotides, such as a framing sequence. The framing sequence can serve various purposes, such as acting as a further annealing region for anti-tags and/or as a sequence informative of the point in time of the synthesis history of the molecule being synthesised.

In certain embodiments, a tag codes for several different reactants. In a subsequent identification step, the structure of the molecule can never-the-less be deduced by taking advantage of the knowledge of the different attachment chemistries, steric

hindrance, deprotection of orthogonal protection groups, etc. In another embodiment, the same tag is used for a group of reactants having a common property, such as a lipophilic nature, molecular weight, or a certain attachment chemistry, etc. In a still further embodiment, each tag is unique, i.e. a similar combination of nucleotides does not identify another reactant. The same of different synthesis methods can employ the same or different type of tags as disclosed herein above.

In some embodiments it can be advantageous to use several different tags for the same reactant. Accordingly, two or more tags identifying the same reactant can optionally carry further information relating to e.g. different reaction conditions.

The identifier oligonucleotide of the final bifunctional complex comprises all the tags necessary for identifying the corresponding molecule. All or part of the sequence of each tag is used to decipher the structure of the reactants that have participated in the formation of the molecule, i.e. the reaction product.

The order of the tags can also be used to determine the order of incorporation of the reactants. This can be of particular interest e.g. when a linear polymer is formed, because the exact sequence of the polymer can be determined by decoding the encoding sequence. Usually, to facilitate the decoding step, tags will further comprise a constant region or a binding region together with the tag sequence identifying a given reactant. The constant region may contain information about the position of the reactant in a synthesis pathway resulting in the synthesis of the molecule.

The identifier oligonucleotide of the bifunctional complex is in a preferred aspect of the invention amplifiable. The capability of being amplified allows for the use of a low amount of bifunctional complex during a selection process. In one embodiment the tag is a sequence of nucleotides which can be amplified using standard techniques like PCR. When two or more tags are present in a linear identifying oligonucleotide, said oligonucleotide generally comprises a certain backbone structure, so as to allow an enzyme to recognise the oligonucleotide as substrate. As an example the back bone structure can be DNA or RNA.

The priming site of a nascent bifunctional complex is capable of receiving a tag. When the tag comprises a polynucleotide sequence, the priming site generally comprises a 3'-OH or 5'-phosphate group, or functional derivatives of such groups. Enzymes which can be used for enzymatic addition of a tag to the priming site include an enzyme selected from polymerase, ligase, and recombinase, and a combination of these enzymes. In some embodiments, an enzyme comprising ligase activity is preferred.

The display oligonucleotide provided in step i) of the above-cited method should be long enough to allow for hybridisation of an anti-tag thereto, c.f. step iv). A desirable length of the display oligonucleotide is from about 3 consecutive nucleotides to about 25 consecutive nucleotides, although longer display oligonucleotides can also be provided. Accordingly, the display oligonucleotide preferably has from 5 to about 20 consecutive nucleotides, for example from 10 to 20 consecutive nucleotides, such as 6 nucleotides, for example 7 nucleotides, such as 8 nucleotides, for example 9 nucleotides, such as 10 nucleotides, for example11 nucleotides, such as 12 nucleotides, for example 13 nucleotides, such as 14 nucleotides, for example 15 nucleotides, such as 16 nucleotides, for example 17 nucleotides, such as 18 nucleotides, for example 19 nucleotides.

Likewise, the each tag should be long enough to allow for hybridisation of one or two anti-tag(s) thereto, c.f. step iii). A desirable length of a tag is from about 3 consecutive nucleotides to about 25 consecutive nucleotides, although longer tags can also be provided. Accordingly, the tags preferably have from 5 to about 20 consecutive nucleotides, such as 6 nucleotides, for example 7 nucleotides, such as 8 nucleotides, for example 9 nucleotides, such as 10 nucleotides, for example11 nucleotides, such as 12 nucleotides, for example 13 nucleotides, such as 14 nucleotides, for example 15 nucleotides, such as 16 nucleotides, for example 17 nucleotides, such as 18 nucleotides, for example 19 nucleotides.

Likewise, the each anti-tag should be long enough to allow for hybridisation of one or two tag(s) thereto, c.f. step iv). A desirable length of an anti-tag is from about 3 consecutive nucleotides to about 25 consecutive nucleotides, although longer anti-tags can also be provided. Accordingly, the anti-tags preferably have from 5 to about 20 consecutive nucleotides, such as 6 nucleotides, for example 7 nucleotides, such as 8 nucleotides, for example 9 nucleotides, such as 10 nucleotides, for example11

nucleotides, such as 12 nucleotides, for example 13 nucleotides, such as 14 nucleotides, for example 15 nucleotides, such as 16 nucleotides, for example 17 nucleotides, such as 18 nucleotides, for example 19 nucleotides.

All or some of the nucleotides of a tag, or an anti-tag, can be involved in the identification of a corresponding reactant. In other words, decoding of an identifier oligonucleotide can be performed by determining the sequence of all or only a part of the identifier oligonucleotide.

In some embodiments of the invention, each tag and each anti-tag constitutes what is often referred to as a “codon” and an “anti-codon”, respectively. These terms are often used in the prior art even though the methods employ split-n-mix technology and not templated reactions. In some embodiments, each tag and each anti-tag comprises one or more “codon(s)” or anti-codon(s)”, respectively, which identifies the corresponding reactant involved in the synthesis of a molecule.

The single-stranded over-hangs resulting from hybridisation of tags and anti-tags can be of any suitable length as long as the over-hang allows for hybridisation of a tag or an anti-tag to the over-hang, c.f. steps vi) and xii). A desirable length for an overhang is from about 3 consecutive nucleotides to about 25 consecutive nucleotides, although longer over-hangs can also be provided for. Accordingly, the over-hangs preferably have from 5 to about 20 consecutive nucleotides, such as 6 nucleotides, for example 7 nucleotides, such as 8 nucleotides, for example 9 nucleotides, such as 10 nucleotides, for example11 nucleotides, such as 12 nucleotides, for example 13 nucleotides, such as 14 nucleotides, for example 15 nucleotides, such as 16 nucleotides, for example 17 nucleotides, such as 18 nucleotides, for example 19 nucleotides.

The identifier oligonucleotide resulting from tag ligation can include or exclude the display oligonucleotide and preferably has a length of from 6 to about 300 consecutive nucleotides, for example from 6 to about 250 consecutive nucleotides, such as from 6 to about 200 consecutive nucleotides, for example from 6 to about 150 consecutive nucleotides, such as from 6 to 100, for example from 6 to 80, such as from 6 to 60, such as from 6 to 40, for example from 6 to 30, such as from 6 to 20, such as from 6 to 15, for example from 6 to 10, such as from 6 to 8, such as 6, for example from 7 to 100, such as from 7 to 80, for example from 7 to 60, such as

from 7 to 40, for example from 7 to 30, such as from 7 to 20, for example from 7 to 15, such as from 7 to 10, such as from 7 to 8, for example 7, for example from 8 to 100, such as from 8 to 80, for example from 8 to 60, such as from 8 to 40, for example from 8 to 30, such as from 8 to 20, for example from 8 to 15, such as from 8 to 10, such as 8, for example 9, for example from 10 to 100, such as from 10 to 80, for example from 10 to 60, such as from 10 to 40, for example from 10 to 30, such as from 10 to 20, for example from 10 to 15, such as from 10 to 12, such as 10, for example from 12 to 100, such as from 12 to 80, for example from 12 to 60, such as from 12 to 40, for example from 12 to 30, such as from 12 to 20, for example from 12 to 15, such as from 14 to 100, such as from 14 to 80, for example from 14 to 60, such as from 14 to 40, for example from 14 to 30, such as from 14 to 20, for example from 14 to 16, such as from 16 to 100, such as from 16 to 80, for example from 16 to 60, such as from 16 to 40, for example from 16 to 30, such as from 16 to 20, such as from 18 to 100, such as from 18 to 80, for example from 18 to 60, such as from 18 to 40, for example from 18 to 30, such as from 18 to 20, for example from 20 to 100, such as from 20 to 80, for example from 20 to 60, such as from 20 to 40, for example from 20 to 30, such as from 20 to 25, for example from 22 to 100, such as from 22 to 80, for example from 22 to 60, such as from 22 to 40, for example from 22 to 30, such as from 22 to 25, for example from 25 to 100, such as from 25 to 80, for example from 25 to 60, such as from 25 to 40, for example from 25 to 30, such as from 30 to 100, for example from 30 to 80, such as from 30 to 60, for example from 30 to 40, such as from 30 to 35, for example from 35 to 100, such as from 35 to 80, for example from 35 to 60, such as from 35 to 40, for example from 40 to 100, such as from 40 to 80, for example from 40 to 60, such as from 40 to 50, for example from 40 to 45, such as from 45 to 100, for example from 45 to 80, such as from 45 to 60, for example from 45 to 50, such as from 50 to 100, for example from 50 to 80, such as from 50 to 60, for example from 50 to 55, such as from 60 to 100, for example from 60 to 80, such as from 60 to 70, for example from 70 to 100, such as from 70 to 90, for example from 70 to 80, such as from 80 to 100, for example from 80 to 90, such as from 90 to 100 consecutive nucleotides.

The length of the identifier oligonucleotide will depend of the length of the individual tags as well as on the number of tags ligated. In some embodiments of the invention it is preferred that the identifier oligonucleotide is attached to a solid or semi-solid support.

The identifier oligonucleotide preferably comprises a string of consecutive nucleotides comprising from 2 to 10 tags, for example from 3 to 10 tags, such as from 4 to 10 tags, for example from 5 to 10 tags, such as from 6 to 10 tags, for example from 7 to 10 tags, such as from 8 to 10 tags, for example from 2 to 9 tags, such as from 2 to 8 tags, for example from 2 to 7 tags, such as from 2 to 6 tags, for example from 2 to 5 tags, such as from 2 to 4 tags, for example 2 or 3 tags, such as from 3 to 9 tags, such as from 3 to 8 tags, for example from 3 to 7 tags, such as from 3 to 6 tags, for example from 3 to 5 tags, such as from 3 to 4 tags, for example from 4 to 9 tags, such as from 4 to 8 tags, for example from 4 to 7 tags, such as from 4 to 6 tags, for example from 4 to 5 tags, such as from 5 to 9 tags, such as from 5 to 8 tags, for example from 5 to 7 tags, such as 5 or 6 tags, for example 2, 3, 4 or 5 tags, such as 6, 7 or 8 tags, for example 9 or 10 tags.

The display oligonucleotide and/or the tags employed in the methods of the present invention in one embodiment preferably comprise or essentially consist of nucleotides selected from the group consisting of deoxyribonucleic acids (DNA), ribonucleic acids (RNA), peptide nucleic acids (PNA), locked nucleic acids (LNA), and morpholinos sequences, including any analog or derivative thereof.

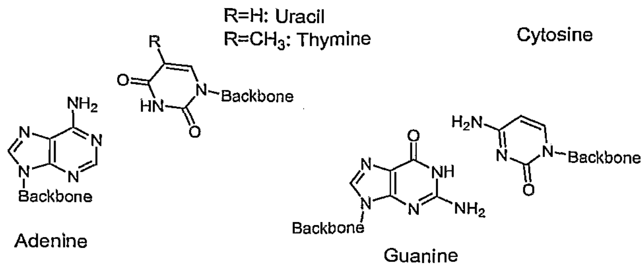
In another embodiment, the display oligonucleotide and/or the tags employed in the methods of the present invention preferably comprise or essentially consist of nucleotides selected from the group consisting of DNA, RNA, PNA, LNA and morpholinos sequence, including any analog or derivative thereof, and the anti-tags preferably comprise or essentially consist of nucleotides selected from the group consisting of DNA, RNA, PNA, LNA and morpholinos sequences, including any analog or derivative thereof.

The nucleic acids useful in connection with the present invention include, but is not limited to, nucleic acids which can be linked together in a sequence of nucleotides, i.e. an oligonucleotide. However, in one embodiment and in order to prevent ligation of anti-tags, c.f. step xiv) and xv), end-positioned nucleic acids of anti-tags do not contain a reactive group, such as a 5'-P or a 3'-OH reactive group, capable of being linked by e.g. an enzyme comprising ligase activity. The priming site of the display oligonucleotide preferably comprises a 3'-OH or 5'-phosphate group, or functional derivatives of such groups, capable of being linked by an enzyme comprising ligase activity.

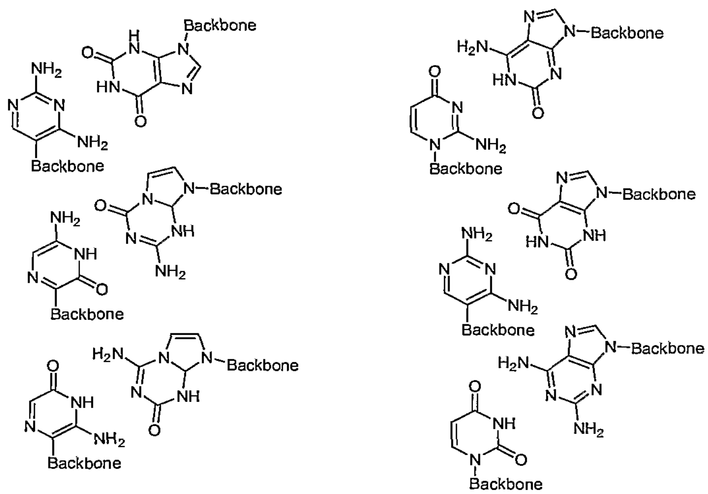
Each nucleotide monomer is normally composed of two parts, namely a nucleobase moiety, and a backbone. The back bone may in some cases be subdivided into a sugar moiety and an internucleoside linker. The nucleobase moiety can be selected among naturally occurring nucleobases as well as non-naturally occurring nucleobases. Thus, "nucleobase" includes not only known purine and pyrimidine hetero-cycles, but also heterocyclic analogues and tautomers thereof. Illustrative examples of nucleobases are adenine, guanine, thymine, cytosine, uracil, purine, xanthine, diaminopurine, 8-oxo-N^6-methyladenine, 7-deazaxanthine, 7-deazaguanine, N^4,N^4-ethanocytosin, N^6,N^6-ethano-2,6-diamino-purine, 5-methylcytosine, 5-(C^3-C^6)-alkynylcytosine, 5-fluorouracil, 5-bromouracil, pseudoisocytosine, 2-hydroxy-5-methyl-4-triazolopyridine, isocytosine, isoguanine, inosine and the "non-natural" nucleobases described in U.S. Pat No. 5,432,272.

The term "nucleobase" is intended to cover these examples as well as analogues and tautomers thereof. Especially interesting nucleobases are adenine, guanine, thymine, cytosine, 5-methylcytosine, and uracil, which are considered as the naturally occurring nucleobases. Examples of suitable specific pairs of nucleobases are shown below:

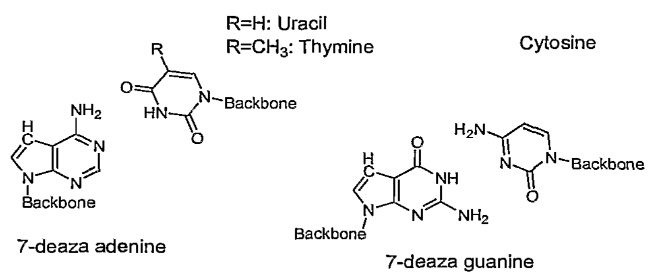
Natural Base Pairs



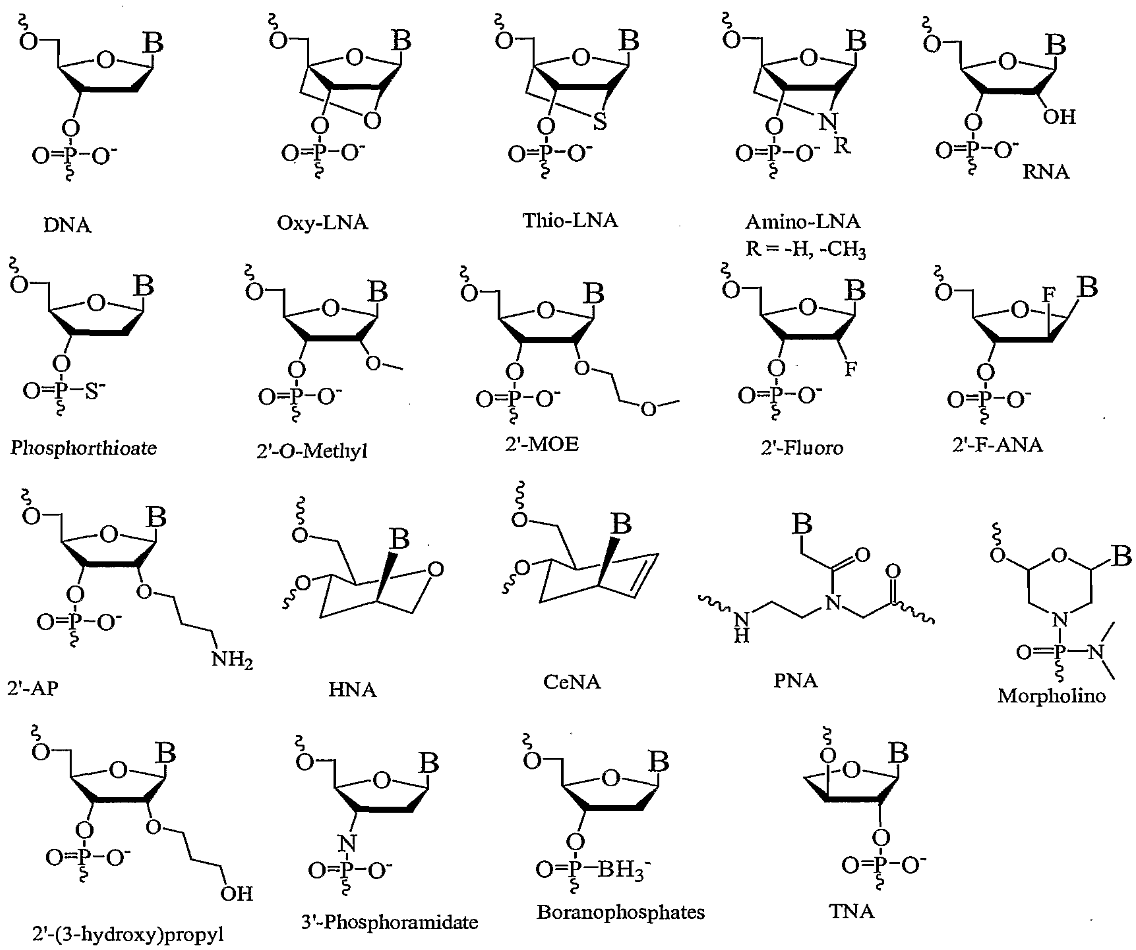
Synthetic Base Pairs



Synthetic purine bases pairring with natural pyrimidines



Suitable examples of backbone units are shown below (B denotes a nucleobase):



The sugar moiety of the backbone is suitably a pentose, but can be the appropriate part of an PNA or a six-member ring. Suitable examples of possible pentoses include ribose, 2'-deoxyribose, 2'-O-methyl-ribose, 2'-flour-ribose, and 2'-4'-O-methylene-ribose (LNA). Suitably the nucleobase is attached to the 1' position of the pentose entity.

An internucleoside linker connects the 3' end of preceding monomer to a 5' end of a succeeding monomer when the sugar moiety of the backbone is a pentose, like ribose or 2-deoxyribose. The internucleoside linkage can be the natural occurring phospodiester linkage or a derivative thereof. Examples of such derivatives include phosphorothioate, methylphosphonate, phosphoramidate, phosphotriester, and phosphodithioate. Furthermore, the internucleoside linker can be any of a number of non-phosphorous-containing linkers known in the art.

Preferred nucleic acid monomers include naturally occurring nucleosides forming part of the DNA as well as the RNA family connected through phosphodiester linkages. The members of the DNA family include deoxyadenosine, deoxyguanosine, deoxythymidine, and deoxycytidine. The members of the RNA family include adenosine, guanosine, uridine, cytidine, and inosine.

It is within the capability of the skilled person in the art to construct the desired design of an oligonucleotide. When a specific annealing temperature is desired it is a standard procedure to suggest appropriate compositions of nucleic acid monomers and the length thereof. The construction of an appropriate design can be assisted by software, such as Vector NTI Suite or the public database at the internet address http://www.nwfsc.noaa.gov/protocols/oligoTMcalc.html. The conditions which allow hybridisation of two oligonucleotides are influenced by a number of factors including temperature, salt concentration, type of buffer, and acidity. It is within the capabilities of the person skilled in the art to select appropriate conditions to ensure that the contacting between two oligonucleotides is performed at hybridisation conditions. The temperature at which two single stranded oligonucleotides forms a duplex is referred to as the annealing temperature or the melting temperature. The melting curve is usually not sharp indicating that the annealing occurs over a temperature range.

Oligonucleotides in the form of tags, anti-tags and display oligonucleotides can be synthesized by a variety of chemistries as is well known. For synthesis of an oligonucleotide on a substrate in the direction of 3' to 5', a free hydroxy terminus is required that can be conveniently blocked and deblocked as needed. A preferred hydroxy terminus blocking group is a dimexothytrityl ether (DMT). DMT blocked termini are first deblocked, such as by treatment with 3% dichloroacetic acid in dichloromethane (DCM) as is well known for oligonucleotide synthesis, to form a free hydroxy terminus.

Nucleotides in precursor form for addition to a free hydroxy terminus in the direction of 3' to 5' require a phosphoramidate moiety having an aminodiisopropyl side chain at the 3' terminus of a nucleotide. In addition, the free hydroxy of the phosphoramidate is blocked with a cyanoethyl ester (OCNET), and the 5' terminus is blocked with a DMT ether. The addition of a 5' DMT-, 3' OCNET-blocked phosphoramidate nucleotide to a free hydroxyl requires tetrazole in acetonitrile

followed by iodine oxidation and capping of unreacted hydroxyls with acetic anhydride, as is well known for oligonucleotide synthesis. The resulting product contains an added nucleotide residue with a DMT blocked 5' terminus, ready for deblocking and addition of a subsequent blocked nucleotide as before.

For synthesis of an oligonucleotide in the direction of 5' to 3', a free hydroxy terminus on the linker is required as before. However, the blocked nucleotide to be added has the blocking chemistries reversed on its 5' and 3' termini to facilitate addition in the opposite orientation. A nucleotide with a free 3' hydroxyl and 5' DMT ether is first blocked at the 3' hydroxy terminus by reaction with TBS-Cl in imidazole to form a TBS ester at the 3' terminus. Then the DMT-blocked 5' terminus is deblocked with DCA in DCM as before to form a free 5' hydroxy terminus. The reagent (N,N-diisopropylamino)(cyanoethyl) phosphonamidic chloride having an aminodiisopropyl group and an OCNET ester is reacted in tetrahydrofuran (THF) with the 5' deblocked nucleotide to form the aminodiisopropyl-, OCNET-blocked phosphonamidate group on the 5' terminus. Thereafter the 3' TBS ester is removed with tetrabutylammonium fluoride (TBAF) in DCM to form a nucleotide with the phosphonamidate-blocked 5' terminus and a free 3' hydroxy terminus. Reaction in base with DMT-Cl adds a DMT ether blocking group to the 3' hydroxy terminus.

The addition of the 3' DMT-, 5' OCNET-blocked phosphonamidated nucleotide to a linker substrate having a free hydroxy terminus then proceeds using the previous tetrazole reaction, as is well known for oligonucleotide polymerization. The resulting product contains an added nucleotide residue with a DMT-blocked 3' terminus, ready for deblocking with DCA in DCM and the addition of a subsequent blocked nucleotide as before.

The identifier oligonucleotide part of a bifunctional complex is formed by addition of a tag or more than one tag to a priming site and/or to a previously added tag using one or more enzymes such as enzymes possessing ligase activity. When one or more further tag(s) are attached to a tag which was added to a nascent bifunctional complex in a previous synthesis round, the addition can produce a linear or a branched identifier oligonucleotide. Preferably, at least one tag of the identifier is attached to the priming site and/or to another tag by an enzymatically catalysed reaction, such as a ligation. Further tag(s) can in principle be attached using

chemical means or enzymatic means. In one embodiment, all tags are attached using an enzymatically catalysed reaction.

The identifier oligonucleotide part of the bifunctional complex is preferably amplifiable. This means that the tags form a sequence of nucleotides capable of being amplified e.g. using a polymerase chain reaction (PCR) techniques.

The tags can be "unique" for a single predetermined reactant, or a given tag can in principle code for several different reactants, in which case the structure of the synthesised molecule can optionally be deduced by taking into account factors such as different attachment chemistries, steric hindrance and deprotection of orthogonal protection groups. It is also possible to use the same or similar tags for a group of reactants having at least one common property in common, such as e.g. lipophilic nature, molecular weight and attachment chemistry.

In one embodiment, two or more tags identifying the same reactant comprise further information related to different reaction conditions used for reacting said reactant. Individual tags can be distinguished from each other by only a single nucleotide, or by two or more nucleotides. For example, when the tag or anti-tag length is 5 nucleotides, more than 100 nucleotide combinations exist in which two or more differences appear between any two tags.

Multiple encoding

In one embodiment, multiple encoding implies that two or more tags are provided in the identifier prior to or subsequent to a reaction between the chemical reactive site and two or more reactants. Multiple encoding has various advantages, such as allowing a broader range of reactions possible, as many compounds can only be synthesis by a three (or more) component reaction because an intermediate between the first reactant and the chemical reactive site is not stable. Other advantages relates to the use of organic solvents and the availability of two or more reactants in certain embodiments.

Thus in a certain aspect of the invention, it relates to a method for obtaining a bifunctional complex comprising a molecule part and a identifier oligonucleotide, wherein the molecule is obtained by reaction of a chemical reactive site with two or

more reactants and the identifier oligonucleotide comprises tag(s) identifying the reactants.

In a certain aspect of the invention, a first reactant forms an intermediate product upon reaction with the chemical reactive site and a second reactant reacts with the intermediate product to obtain the molecule or a precursor thereof. In another aspect of the invention, two or more reactants react with each other to form an intermediate product and the chemical reactive site reacts with this intermediate product to obtain the molecule or a precursor thereof. The intermediate product can be obtained by reacting the two or more reactants separately and then in a subsequent step reacting the intermediate product with the chemical reactive site. Reacting the reactants in a separate step provide for the possibility of using conditions the tags would not withstand. Thus, in case the identifier oligonucleotide comprises nucleic acids, the reaction between the reactant can be conducted at conditions that otherwise would degrade the nucleic acid.

The reactions can be carried out in accordance with the scheme shown below. The scheme shows an example in which the identifying tags for two reactants and the chemical reactive site (scaffold) attached to the chemical reaction site are provided in separate compartments. The compartments are arranged in an array, such as a microtiter plate, allowing for any combination of the different acylating agents and the different alkylating agents.

Starting situation:

Alkylating agents / Acylating agents	**A**	**B**	**C**	...
1	Tagx11-X	Tagx12-X	Tagx13-X	...
2	Tagx21-X	Tagx22-X	Tagx23-X	...
3	Tagx31-X	Tagx32-X	Tagx33-X	...
...	...	...	...	...

X denotes a chemical reaction site such as a scaffold.

The two reactants are either separately reacted with each other in any combination or subsequently added to each compartment in accordance with the tags of the identifier oligonucleotide or the reactants can be added in any order to each

compartment to allow for a direct reaction. The scheme below shows the result of the reaction.

Plate of products

Alkylating agents / Acylating agents	**A**	**B**	**C**	...
1	Tagx11-XA1	Tagx12-XB1	Tagx13-XC1	...
2	Tagx21-XA2	Tagx22-XB2	Tagx23-XC2	...
3	Tagx31-XA3	Tagx32-XB3	Tagx33-XC3	...
...	...	...	...	...

As an example XA2 denotes molecule XA2 in its final state, i.e. fully assembled from fragments X, A and 2.

The identifier oligonucleotide comprising the two or more tags identifying the reactants, can in principle be prepared in any suitable way either before or after the reaction. In one embodiment of the invention, each of the identifier oligonucleotides are synthesised by standard phosphoramidite chemistry. In another aspect the tags are pre-prepared and assembled into the final identifier oligonucleotide by chemical or enzymatic ligation.

Various possibilities for chemical ligation exist. Suitable examples include that
a) a first oligonucleotide end comprises a 3'-OH group and the second oligonucleotide end comprises a 5'-phosphor-2-imidazole group. When reacted a phosphodiester internucleoside linkage is formed,
b) a first oligonucleotide end comprising a phosphoimidazolide group and the 3'-end and a phosphoimidazolide group at the 5'-and. When reacted together a phosphodiester internucleoside linkage is formed,
c) a first oligonucleotide end comprising a 3'-phosphorothioate group and a second oligonucleotide comprising a 5'-iodine. When the two groups are reacted a 3'-O-P(=O)(OH)-S-5' internucleoside linkage is formed, and
d) a first oligonucleotide end comprising a 3'-phosphorothioate group and a second oligonucleotide comprising a 5'-tosylate. When reacted a 3'-O-P(=O)(OH)-S-5' internucleoside linkage is formed.

<u>Enzymes</u>

The identifier oligonucleotide of a nascent bifunctional complex involves the addition of at least one tag to a priming site using one or more enzymes. Further tags can be attached to a previous tag so as to produce a linear or branched identifier oligonucleotide. One or more enzymes are used for at least one reaction involving one or more identifier oligonucleotide tags. Enzymes are in general substrate specific, entailing that the enzymatic addition of a tag to a priming site, or to another tag, is not likely to interfere with the synthesis of a molecule. Enzymes can be active in both aqueous and organic solvents.

As long as at least one tag of the identifier is attached to the priming site or to another tag by an enzymatic reaction, further tags can be added using either chemical means or the same or different enzymatic means. In one embodiment, all of the tags are added to the priming site and/or to each other using the same or different enzymatically catalysed reaction(s).

In one embodiment, addition of a tag to the priming site, or to a tag having reacted with the priming site or another tag in a previous synthesis round, can involve an enzymatic extension reaction. The extension reaction can be performed by a polymerase or a ligase, or a combination thereof. The extension using a polymerase is suitably conducted using a tag hybridised to an anti-tag oligonucleotide as template. The substrate is usually a blend of triphosphate nucleotides selected from the group comprising dATP, dGTP, dTTP, dCTP, rATP, rGTP, rTTP, rCTP, rUTP.

In a different embodiment, a ligase is used for the addition of a tag using one or more oligonucleotides as substrates. The ligation can be performed in a single stranded or a double stranded state depending on the enzyme used. In general it is preferred to ligate tags in a double stranded state, i.e. tag oligonucleotides to be ligated together are kept together by a complementing oligonucleotide (anti-tag), which complements the ends of the two tag oligonucleotides to be ligated.

Substrates for ligases are oligo- and polynucleotides, i.e. nucleic acids comprising two or more nucleotides. An enzymatic ligation can be performed in a single or double stranded fashion. When a single stranded ligation is performed, a 3' OH group of a first nucleic acid is ligated to a 5' phosphate group of a second nucleic acid. A double stranded ligation uses a third oligonucleotide complementing a part of

the 3' end and 5' end of the first and second nucleic acid to assist in the ligation. Generally, it is preferred to perform a double stranded ligation. Only tags are ligated. Anti-tags are not ligated as they do not, in one embodiment, comprise a reactive group, such as a 5'-P or a 3'-OH, or variants or derivatives thereof, enabling enzymatic ligation. In another embodiment, anti-tags do not abut to each other but are physically separated by hybridisation to parts of tag oligonucleotides which are separated from each other. This is illustrated in Fig. 3.

In some embodiments of the invention, a combination of polymerase transcription and ligational coupling is used. As an example, a gap in an otherwise double stranded nucleic acid can be filled-in by a polymerase and a ligase can ligate the tag portion of the extension product.

Examples of suitable polymerases include DNA polymerase, RNA polymerase, Reverse Transcriptase, DNA ligase, RNA ligase, Taq DNA polymerase, Pfu polymerase, Vent polymerase, HIV-1 Reverse Transcriptase, Klenow fragment, or any other enzyme that will catalyze the incorporation of complementing elements such as mono-, di- or polynucleotides. Other types of polymerases that allow mismatch extension could also be used, such for example DNA polymerase η (Washington et al., (2001) JBC 276: 2263-2266), DNA polymerase ι (Vaisman et al., (2001) JBC 276: 30615-30622), or any other enzyme that allow extension of mismatched annealed base pairs.

Suitable examples of ligases include Taq DNA ligase, T4 DNA ligase, T4 RNA ligase, T7 DNA ligase, and *E. coli* DNA ligase. The choice of the ligase depends, among other things, on the design of the ends to be joined together. Thus, if the ends are blunt, T4 RNA ligase can be preferred, while a Taq DNA ligase can be preferred for a sticky end ligation, i.e. a ligation in which an overhang on each end is a complement to each other.

Chemical reaction site, reactants and reactive groups

The chemical reaction site can comprise a single reactive group or two or more reactive groups. In preferred embodiments, the chemical reaction site comprises 3 or more reactive groups. The plurality of reactive groups of a chemical reaction site

can each react with one or more reactants each comprising one or more reactive groups linked to one or more chemical entities.

Reactive groups of the chemical reaction site are in principle no different from reactive groups of complementary reactants capable of reacting with each other under conditions allowing such a reaction to occur. Examples of reactive groups of chemical reaction sites and complementary reactants are listed e.g. in figure 58 and in the detailed disclosure of the invention herein below.

Chemical reaction site reactive groups can be selected a variety of from well known reactive groups, such as e.g. hydroxyl groups, thiols, optionally substituted or activated carboxylic acids, isocyanates, amines, esters, thioesters, and the like. Further non-limiting examples of reactive group reactions are e.g. Suzuki coupling, Heck coupling, Sonogashira coupling, Wittig reaction, alkyl lithium-mediated condensations, halogenation, SN2 displacements (for example, N, O, S), ester formation, and amide formation, as well as other reactions and reactive groups that can be used to generate chemical entities, such as those presented herein.

In general, the chemical reaction site and reactants capable of reacting with the chemical reaction site, i.e. complementary reactants, can in principle be any chemical compounds which are complementary, that is the reactive groups of the entities in question must be able to react. Typically, a reactant can have a single reactive group or more than one reactive group, such as at least two reactive groups, although it is possible that some of the reactants used will have more than two reactive groups each. This will be the case when branched molecules are synthesised.

The number of reactive groups on present on a reactant and/or a chemical reaction site is suitably from 1 to 10, for example 1, such as 2, for example 3, such as 4, for example 5, such as 6, for example 7, such as 8, for example 9, such as from 2 to 4, for example from 4 to 6, such as from 6 to 8, for example from 8 to 10, such as from 2 to 6, for example from 6 to 10, such as from 3 to 6, for example from 6 to 9, such as from 4 to 6, for example from 6 to 10 reactive groups present on the chemical reaction site and/or a reactant capable of reacting with the chemical reaction site and/or with another reactant.

Reactive groups on two different reactants should be complementary, i. e., capable of reacting to form a covalent bond, optionally with the concomitant loss of a small molecular entity, such as water, HCl, HF, and so forth.

Two reactive groups are complementary if they are capable of reacting together to form a covalent bond. Complementary reactive groups of two reactants can react, for example, via nucleophilic substitution, to form a covalent bond. In one embodiment, one member of a pair of complementary reactive groups is an electrophilic group and the other member of the pair is a nucleophilic group. Examples of suitable electrophilic reactive groups include reactive carbonyl groups, such as acyl chloride groups, ester groups, including carbonylpentafluorophenyl esters and succinimide esters, ketone groups and aldehyde groups; reactive sulfonyl groups, such as sulfonyl chloride groups, and reactive phosphonyl groups. Other electrophilic reactive groups include terminal epoxide groups, isocyanate groups and alkyl halide groups. Suitable nucleophilic reactive groups include, but is not limited to, primary and secondary amino groups and hydroxyl groups and carboxyl groups.

Accordingly, complementary electrophilic and nucleophilic reactive groups include any two groups which react via nucleophilic substitution under suitable conditions to form a covalent bond. A variety of suitable bond-forming reactions are known in the art. See, for example, March, Advanced Organic Chemistry, fourth edition, New York: John Wiley and Sons (1992), Chapters 10 to 16; Carey and Sundberg, Advanced Organic Chemistry, Part B, Plenum (1990), Chapters1-11 ; and Collman etal., Principles and Applications of Organotransition Metal Chemistry, University Science Books, Mill Valley, Calif. (1987), Chapters 13 to 20; each of which is incorporated herein by reference in its entirety.

Further suitable complementary reactive groups are set forth herein below. One of skill in the art can readily determine other reactive group pairs that can be used in the present method, such as, but not limited to, reactive groups capable of facilitating the reactions illustrated in Table 1.

In some embodiments, the reactive groups of the chemical reaction site and/or the reactive group(s) of one or more reactants reacting with each other and/or with the chemical reaction site are preferably selected from the group consisting of:

a) activated carboxyl groups, reactive sulfonyl groups and reactive phosphonyl groups, or a combination thereof, and complementary primary or secondary amino groups; the complementary reactive groups react under suitable conditions to form amide, sulfonamide and/or phosphonamidate bonds;

b) epoxide groups and complementary primary and/or secondary amino groups; a reactant comprising one or more epoxide reactive group(s) can react with one or more amine-group(s) of a complementary reactant under suitable conditions to form one or more carbon-nitrogen bond(s), resulting e.g. in a beta-amino alcohol;

c) aziridine groups and complementary primary or secondary amino groups; under suitable conditions, a reactant comprising one or more aziridine-group(s) can react with one or more amine-group(s) of a complementary reactant to form one or more carbon-nitrogen bond(s), resulting e.g. in a 1,2-diamine;

d) isocyanate groups and complementary primary or secondary amino groups, a reactant comprising one or more isocyanate-group(s) can react with one or more amino-group(s) of a complementary reactant under suitable conditions to form one or more carbon-nitrogen bond(s), resulting e.g. in a urea group;

e) isocyanate groups and complementary hydroxyl groups; a reactant comprising one or more isocyanate-group(s) can react with a complementary reactant comprising one or more hydroxyl-groups under suitable conditions to form one or more carbon-oxygen bond(s), resulting e.g. in a carbamate group.

f) amino groups and complementary carbonyl groups; a reactant comprising one or more amino groups can react with a complementary reactant comprising one or more carbonyl-group(s), such as aldehyde and/or a ketone group(s); the amines can react with such groups via reductive amination to form e.g. a carbon-nitrogen bond;

g) phosphorous ylide groups and complementary aldehyde and/or ketone groups; A reactant comprising a phosphorus-ylide-group can react with an aldehyde and/or a ketone-group of a complementary reactant under suitable conditions to form e.g. a carbon-carbon double bond, resulting e.g. in an alkene;

h) complementary reactive groups can react via cycloaddition to form a cyclic structure; an example of such complementary reactive groups are alkynes and organic azides, which can react under suitable conditions to form a triazole ring structure - suitable conditions for such reactions are known in the art and include those disclosed in WO 03/101972, the entire contents of which are incorporated by reference herein;

i) the complementary reactive groups are alkyl halide groups and one or more nucleophile group(s), such as, but not limited to, nucleophile groups selected from the group consisting of amino groups, hydroxyl groups and carboxyl group; such groups react under suitable conditions to form a carbon-nitrogen bond (alkyl halide plus amine) or carbon oxygen bond (alkyl halide plus hydroxyl or carboxyl group);

j) the complementary functional groups are halogenated heteroaromatic groups and one or more nucleophile group(s), the reactants are linked under suitable conditions via aromatic nucleophilic substitution; suitable halogenated heteroaromatic groups include chlorinated pyrimidines, triazines and purines, which react with nucleophiles, such as amines, under mild conditions in aqueous solution.

As will be clear from the above, a large variety of chemical reactions may optionally be used for the formation of one or more covalent bonds between a reactant and one or more chemical reaction sites and a large variety of chemical reactions may optionally beused for the formation of one or more covalent bonds between one or more reactants.

Thus, reactions such as those listed in March's Advanced Organic Chemistry, Organic Reactions, Organic Syntheses, organic text books, journals such as Journal of the American Chemical Society, Journal of Organic Chemistry, Tetrahedron, etc., and Carruther's Some Modern Methods of Organic Chemistry can be used. The chosen reactions preferably are compatible with nucleic acids such as DNA or RNA or are compatible with the modified nucleic acids used as the template. Reactions useful in stage 1 and stage 2 synthesis include, for example, substitution reactions, carbon-carbon bond forming reactions, elimination reactions, acylation reactions, and addition reactions. An illustrative but not exhaustive list of aliphatic nucleophilic substitution reactions useful in the present invention includes, for example, SN2 reactions, SNI reactions, SNi reactions, allylic rearrangements, nucleophilic

substitution at an aliphatic trigonal carbon, and nucleophilic substitution at a vinylic carbon. Specific aliphatic nucleophilic substitution reactions with oxygen nucleophiles include, for example, hydrolysis of alkyl halides, hydrolysis of gen-dihalides, hydrolysis of 1,1,1- trihalides, hydrolysis of alkyl esters or inorganic acids, hydrolysis of diazo ketones, hydrolysis of acetal and enol ethers, hydrolysis of epoxides, hydrolysis of acyl halides, hydrolysis of anhydrides, hydrolysis of carboxylic esters, hydrolysis of amides, alkylation with alkyl halides (Williamson Reaction), epoxide formation, alkylation with inorganic esters, alkylation with diazo compounds, dehydration of alcohols, transetherification, alcoholysis of epoxides, alkylation with onium salts, hydroxylation of silanes, alcoholysis of acyl halides, alcoholysis of anhydrides, esterfication of carboxylic acids, alcoholysis of carboxylic esters (transesterfication), alcoholysis of amides, alkylation of carboxylic acid salts, cleavage of ether with acetic anhydride, alkylation of carboxylic acids with diazo compounds, acylation of carboxylic acids with acyl halides; acylation of carlpoxylic acids with carboxylic acids, formation of oxoniiim salts, preparation of peroxides arid hydroperoxides, preparation of inorganic esters (e.g., nitrites, nitrates, sulfonates), preparation of alcohols from amines, arid preparation of mixed organic-inorganic anhydrides.

Specific aliphatic nucleophilic substitution reactions with sulfur nucleophiles, which tend to be better nucleophiles than their oxygen analogs, include, for example, attack by SH at an alkyl carbon to form thiols, attack by S at an alkyl carbon to form thioethers, attack by SH or SR at an acyl carbon, formation of disulfides,, formation of Bunte salts, alkylation of sulfuric acid salts, and formation of alkyl thiocyanates.

Aliphatic nucleophilic substitution reactions with nitrogen nucleophiles include, for example, alkylation of amines, /V-ar[gamma]lation of amines, replacement of a hydroxy by an amino group, transamination, transamidation, alkylation of amines with diazo compounds, animation of epoxides, amination of oxetanes, amination of aziridines, amination of alkanes, formation of isocyanides, acylation of amines by acyl halides, acylation of amines by anhydrides, acylation of amines by carboxylic acids, acylation of amines by carboxylic esters, acylation of amines by amides, acylation of amines by other acid derivatives, /V-alkylation or /V-arylation of amides and imides, /V-acylation of amides and imides, formation of aziridines from epoxides, formation of nitro compounds, formation of azides, formation of isocyanates and isothiocyanates, and formation of azoxy compounds. Aliphatic

nucleophilic substitution reactions with halogen nucleophiles include, for example, attack at an alkyl carbon, halide exchange, formation of alkyl halides from esters of sulfuric and sulfonic acids, formation of alkyl halides from alcohols, formation of alkyl halides from ethers, formation of halohydrins from epoxides, cleavage of carboxylic esters with lithium iodide, conversion of diazo ketones to alpha-halo ketones, conversion of amines to halides, conversion of tertiary amines to cyanamides (the von Braun reaction), formation of acyl halides from carboxylic acids, and formation of acyl halides from acid derivatives.

Aliphatic nucleophilic substitution reactions using hydrogen as a nudeophile include, for example, reduction of alkyl halides, reduction of tosylates, other sulfonates, and similar compounds, hydrogenolysis of alcohols, hydrogenolysis of esters (Barton-McCombie reaction), hydrogenolysis of nitriles, replacement of alkoxyl by hydrogen, reduction of epoxides, reductive cleavage of carboxylic esters, reduction of a C-N bond, desulfurization, reduction of acyl halides, reduction of carboxylic acids, esters, and anhydrides to aldehydes, and reduction of amides to aldehydes.

Although certain carbon nucleophiles may be too nucleophilic and/or basic to be used in certain embodiments of the invention, aliphatic nucleophilic substitution reactions using carbon nucleophiles include, for example, coupling with silanes, coupling of alkyl halides (the Wurtz reaction), the reaction of alkyl halides and sulfonate esters with Group I (I A), and II (II A) organometallic reagents, reaction of alkyl halides and sulfonate esters with organocuprates, reaction of alkyl halides and sulfonate esters with other organometallic reagents; allylic and propargylic coupling with a halide substrate, coupling of organometallic reagents with esters of sulfuric and sulfonic acids, sulfoxides, and sulfones, coupling involving alcohols, coupling of organometallic reagents with carboxylic esters, coupling of organometallic reagents with compounds containing an esther linkage, reaction of organometallic reagents with epoxides, reaction of organometallics with aziridine, alkylation at a carbon bearing an active hydrogen, alkylation of ketones, nitriles, and carboxylic esters, alkylation of carboxylic acid salts, alkylation at a position alpha to a heteroatom (alkylation of 1,3-dithianes), alkylation of dihydro-l,3-oxazine (the Meyers synthesis of aldehydes, ketones, and carboxylic acids), alkylation with trialkylboranes, alkylation at an alkynyl carbon, preparation of nitriles, direct conversion of alkyl halides to aldehydes and ketones, conversion of alkyl halides, alcohols, or alkanes to carboxylic acids and their derivatives, the conversion of acyl halides to ketones

with organometallic compounds, the conversion of anhydrides, carboxylic esters, or amides to ketones with organometallic compounds, the coupling of acyl halides, acylation at a carbon bearing an active hydrogen, acylation of carboxylic esters by carboxylic esters (the Claisen and Dieckmann condensation), acylation of ketones and nitriles with carboxylic esters, acylation of carboxylic acid salts, preparation of acyl cyanides, and preparation of diazo ketones, ketonic decarboxylation. Reactions which involve nucleophilic attack at a sulfonyl sulfur atom may also be used in the present invention and include, for example, hydrolysis of sulfonic acid derivatives (attack by OH), formation of sulfonic esters (attack by OR), formation of sulfonamides (attack by nitrogen), formation of sulfonyl halides (attack by halides), reduction of sulfonyl chlorides (attack by hydrogen), and preparation of sulfones (attack by carbon).

Aromatic electrophilic substitution reactions may also be used in stage 1 and stage 2 synthesis schemes. Hydrogen exchange reactions are examples of aromatic electrophilic substitution reactions that use hydrogen as the electrophile. Aromatic electrophilic substitution, reactions which use nitrogen electrophiles include, for example, nitration and nitro-dehydrogenation, nitrosation of nitroso-de-hydrogenation, diazonium coupling, direct introduction of the diazonium group, and amination or amino-dehydrogenation. Reactions of this type with sulfur electrophiles include, for example, sulfonation, sulfo-dehydrogenation, halosulfonation, halosulfo-dehydrogenation, sulfurization, and sulfonylation. Reactions using halogen electrophiles include, for example, halogenation, and halo-dehydrogenation. Aromatic electrophilic substitution reactions with carbon electrophiles include, for example, Friedel-Crafts alkylation, alkylation, alkyl- dehydrogenation, Friedel-Crafts arylation (the Scholl reaction), Friedel-Crafts acylation, formylation with disubstituted formamides, formylation with zinc cyanide and HCl (the Gatterman reaction), formylation with chloroform (the Reimer-Tiemami reaction), other formylations, formyl- dehydrogenation, carboxylation with carbonyl halides, carboxylation with carbon dioxide (the Kolbe- Schmitt reaction), amidation with isocyanates, [Lambda]/-alkylcarbamoyl-dehydrogenation, hydroxyalkylation, hydroxyalkyl-dehydrogenation, cyclodehydration of aldehydes and ketones, haloalkylation, halo-dehydrogenation, aminoalkylation, amidoalkylation, dialkylaminoalkylation, dialkylamino-dehydrogenation, thioalkylation, acylation with nitriles (the Hoesch reaction), cyanation, and cyano-de hydrogenation. Reactions using oxygen electrophiles include, for example, hydroxylation and hydroxy-dehydrogenation.

Rearrangement reactions include, for example, the Fries rearrangement, migration of a nitro group, migration of a nitroso group (the Fischer-Hepp Rearrangement), migration of an arylazo group, migration of a halogen (the Orton rearrangement), migration of an alkyl group, etc. Other reaction on an aromatic ring include the reversal of a Friedel-Crafts alkylation, decarboxylation of aromatic aldehydes, decarboxylation of aromatic acids, the Jacobsen reaction, deoxygenation, desulfonation, hydro-desulfonation, dehalogenation, hydro-dehalogenation, and hydrolysis of organometallic compounds.

Aliphatic electrophilic substitution reactions are also useful. Reactions using the SEI, SE2 (front), SE2 (back), SEi, addition-elimination, and cyclic mechanisms can be used in the present invention. Reactions of this type with hydrogen as the leaving group include, for example, hydrogen exchange (deuterio-de-hydrogenation, deuteriation), migration of a double bond, and keto-enol tautomerization. Reactions with halogen electrophiles include, for example, halogenation of aldehydes and ketones, halogenation of carboxylic acids and acyl halides, and halogenation of sulfoxides and sulfones. Reactions with nitrogen electrophiles include, for example, aliphatic diazonium coupling, nitrosation at a carbon bearing an active hydrogen, direct formation of diazo compounds, conversion of amides to alpha-azido amides, direct amination at an activated position, and insertion by nitrenes. Reactions with sulfur or selenium electrophiles include, for example, sulfenylation, sulfonation, and selenylation of ketones and carboxylic esters. Reactions with carbon electrophiles include, for example, acylation at an aliphatic carbon, conversion of aldehydes to beta-keto esters or ketones, cyanation, cyano-de-hydrogenation, alkylation of alkanes, the Stork enamine reaction, and insertion by carbenes. Reactions with metal electrophiles include, for example, metalation with organometallic compounds, metalation with metals and strong bases, and conversion of enolates to silyl enol ethers. Aliphatic electrophilic substitution reactions with metals as leaving groups include, for example, replacement of metals by hydrogen, reactions between organometallic reagents and oxygen, reactions between organometallic reagents and peroxides, oxidation of trialkylboranes to borates, conversion of Grignard reagents to sulfur compounds, halo-demetalation, the conversion of organometallic compounds to amines, the conversion of organometallic compounds to ketones, aldehydes, carboxylic esters and amides, cyano-de-metalation, transmetalation with a metal, transmetalation with a metal halide, transmetalation with an organometallic

compound, reduction of alkyl halides, metallo-de- halogenation, replacement of a halogen by a metal from an organometallic compound, decarboxylation of aliphatic acids, cleavage of aikoxides, replacement of a carboxyl group by an acyl group, basic cleavage of beta-keto esters and beta-diketones, haloform reaction, cleavage of non-enolizable ketones, the Haller-Bauer reaction, cleavage of alkanes, decyanation, and hydro-de-cyanation. Electrophilic substitution reactions at nitrogen include, for example, diazotization, conversion of hydrazines to azides, /V-nitrosation, N- nitroso-de-hydrogenation, conversion of amines to azo compounds, /V-halogenation, /V-halo-de- hydrogenation, reactions of amines with carbon monoxide, and reactions of amines with carbon dioxide. Aromatic nudeophilic substitution reactions may also be used in the present invention. Reactions proceeding via the SNAr mechanism, the SNI mechanism, the benzyne mechanism, the SRN1 mechanism, or other mechanism, for example, can be used. Aromatic nudeophilic substitution reactions with oxygen nucleophiles include, for example, hydroxy-de-halogenation, alkali fusion of sulfonate salts, and replacement of OR or OAr. Reactions with sulfur nucleophiles include, for example, replacement by SH or SR. Reactions using nitrogen nucleophiles include, for example, replacement by NH2, NHR, or NR2, and replacement of a hydroxy group by an amino group: Reactions with halogen nucleophiles include, for example, the introduction halogens. Aromatic nudeophilic substitution reactions with hydrogen as the nucleophile include, for example, reduction of phenols and phenolic esters and ethers, and reduction of halides and nitro compounds. Reactions with carbon nucleophiles include, for example, the Rosenmund-von Braun reaction, coupling of organometallic compounds with aryl halides, ethers, and carboxylic esters, arylation at a carbon containing an active hydrogen, conversions of aryl substrates to carboxylic acids, their derivatives, aldehydes, and ketones, and the Ullmann reaction. Reactions with hydrogen as the leaving group include, for example, alkylation, arylation, and amination of nitrogen heterocycles. Reactions with N2<+> as the leaving group include, for example, hydroxy-de- diazoniation, replacement by sulfur-containing groups, iodo-de-diazoniation, and the Schiemann reaction. Rearrangement reactions include, for example, the von Richter rearrangement, the Sommelet-Hauser rearrangement, rearrangement of aryl hydroxylamines, and the Smiles rearrangement. Reactions involving free radicals can also be used, although the free radical reactions used in nudeotide-templated chemistry should be carefully chosen to avoid modification or cleavage of the nucleotide template. With that limitation, free radical substitution reactions can be used in the present invention.

Particular free radical substitution reactions include, for example, substitution by halogen, halogenation at an alkyl carbon, allylic halogenation, benzylic halogenation, halogenation of aldehydes, hydroxylation at an aliphatic carbon, hydroxylation at an aromatic carbon, oxidation of aldehydes to carboxylic acids, formation of cyclic ethers, formation of hydroperoxides, formation of peroxides, acyloxylation, acyloxy-de-hydrogenation, chlorosulfonation, nitration of alkanes, direct conversion of aldehydes to amides, amidation and amination at an alkyl carbon, simple coupling at a susceptible position, coupling of alkynes, arylation of aromatic compounds by diazonium salts, arylation of activated alkenes by diazonium salts (the Meerwein arylation), arylation and alkylation of alkenes by organopalladium compounds (the Heck reaction), arylation and alkylation of alkenes by vinyltin compounds (the StHle reaction), alkylation and arylation of aromatic compounds by peroxides, photochemical arylation of aromatic compounds, alkylation, acylation, and carbalkoxylation of nitrogen heterocydes. Particular reactions in which N2<+> is the leaving group include, for example, replacement of the diazonium group by hydrogen, replacement of the diazonium group by chlorine or bromine, nitro-de- diazoniation, replacement of the diazonium group by sulfur-containing groups, aryl dimerization with diazonium salts, methylation of diazonium salts, vinylation of diazonium salts, arylation of diazonium salts, and conversion of diazonium salts to aldehydes, ketones, or carboxylic acids. Free radical substitution reactions with metals as leaving groups include, for example, coupling of Grignard reagents, coupling of boranes, and coupling of other organometallic reagents. Reaction with halogen as the leaving group are included. Other free radical substitution reactions with various leaving groups include, for example, desulfurization with Raney Nickel, conversion of sulfides to organolithium compounds, decarboxylase dimerization (the Kolbe reaction), the Hunsdiecker reaction, decarboxylative allylation, and decarbonylation of aldehydes and acyl halides.

Reactions involving additions to carbon-carbon multiple bonds are also used in the stage 1 and stage 2 synthesis schemes. Any mechanism may be used in the addition reaction including, for example, electrophilic addition, nucleophilic addition, free radical addition, and cyclic mechanisms. Reactions involving additions to conjugated systems can also be used. Addition to cyclopropane rings can also be utilized. Particular reactions include, for example, isomerization, addition of hydrogen halides, hydration of double bonds, hydration of triple bonds, addition of

alcohols, addition of carboxylic acids, addition of H2S and thiols, addition of ammonia and amines, addition of amides, addition of hydrazoic acid, hydrogenation of double and triple bonds, other reduction of double and triple bonds, reduction of the double and triple bonds of conjugated systems, hydrogenation of aromatic rings, reductive cleavage of cyclopropanes, hydroboration, other hydrometalations, addition of alkanes, addition of alkenes and/or alkynes to alkenes and/or alkynes (e.g., pi-cation cyclization reactions, hydro-alkenyl-addition), ene reactions, the Michael reaction, addition of organometallics to double and triple bonds not conjugated to carbonyls, the addition of two alkyl groups to an alkyne, 1,4-addition of organometallic compounds to activated double bonds, addition of boranes to activated double bonds, addition of tin and mercury hydrides to activated double bonds, acylation of activated double bonds and of triple bonds, addition of alcohols, amines, carboxylic esters, aldehydes, etc., carbonylation of double and triple bonds, hydrocarboxylation, hydroformylation, addition of aldehydes, addition of HCN, addition of silanes, radical addition, radical cydization, halogenation of double and triple bonds (addition of halogen, halogen), halolactonization, halolactamization, addition of hypohalous acids and hypohalites (addition of halogen, oxygen), addition of sulfur compounds (addition of halogen, sulfur), addition of halogen and an amino group (addition of halogen, nitrogen), addition of NOX and NO2X (addition of halogen, nitrogen), addition of XN3 (addition of halogen, nitrogen), addition of alkyl halides (addition of halogen, carbon), addition of acyl halides (addition of halogen, carbon), hydroxylation (addition of oxygen, oxygen) (e.g., asymmetric dihydroxylation reaction with OSO4), dihydroxylation of aromatic rings, epoxidation (addition of oxygen, oxygen) (e.g., Sharpless asymmetric epoxidation), photooxidation of dienes (addition of oxygen, oxygen), hydroxysulfenylation (addition of oxygen, sulfur), oxyamination (addition of oxygen, nitrogen), diamination (addition of nitrogen, nitrogen), formation of aziridines (addition of nitrogen), aminosulferiylation (addition of nitrogen, sulfur), acylacyloxylation and acylamidation (addition of oxygen, carbon or nitrogen, carbon), 1,3-dipolar addition; (addition of oxygen, nitrogen, carbon), Diels-Alder reaction, heteroatom Diels-Alder reaction, all carbon 3 +2 cycloadditions, dimerization of alkenes, the addition of carbenes and carbenoids to double and triple bonds, trimerization and tetramerization of alkynes, and other cycloaddition reactions.

In addition to reactions involving additions to carbon-carbon multiple bonds, addition reactions to carbon-hetero multiple bonds can be used in nucleotide-templated

chemistry. Exemplary reactions include, for example, the addition of water to aldehydes and ketones (formation of hydrates), hydrolysis of carbon-nitrogen double bond, hydrolysis of aliphatic nitro compounds, hydrolysis of nitriles, addition of alcohols and thiols to aldehydes and ketones, reductive alkylation of alcohols, addition of alcohols to isocyanates, alcoholysis of nitriles, formation of xanthates, addition of H2S and thiols to carbonyl compounds, formation of bisulfite addition products, addition of amines to aldehydes and ketones, addition of amides to aldehydes, reductive alkylation of ammonia or amines, the Mannich reaction, the addition of amines to isocyanates, addition of ammonia or amines to nitriles, addition of amines to carbon disulfide and carbon dioxide, addition of hydrazine derivative to carbonyl compounds, formation of oximes, conversion of aldehydes to nitriles, formation of gem-dihalides from aldehydes and ketones, reduction of aldehydes and ketones to alcohols, reduction of the carbon-nitrogen double bond, reduction of nitriles to amines, reduction of nitriles to aldehydes, addition of Grignard reagents and organolithium reagents to aldehydes and ketones, addition of other organometallics to aldehydes and ketones, addition of trialkylallylsilanes to aldehydes and ketones, addition of conjugated alkenes to aldehydes (the Baylis-Billmah reaction), the Reformatsky reaction, the conversion of carboxylic acid salts to ketones with organometallic compounds, the addition of Grignard reagents to acid derivatives, the addition of Organometallic compounds to CO2 and CS2, addition of organometallic compounds to C=IM compounds, addition of carbenes and diazoalkanbs to C=N compounds, addition of Grignard reagents to nitriles and isocyanates, the Aldol reaction, Mukaiyama Aldol and related reactions, Aldol-type reactions between carboxylic esters or amides and aldehydes or ketones, the Knoevenagel reaction (e.g., the Nef reaction, the Favorskii reaction), the Peterson alkenylation reaction, the addition of active hydrogen compounds to CO2 and CS2, the Perkin reaction, Darzens glycidic ester condensation, the Tollens reaction, the Wittig reaction, the Tebbe alkenylation, the Petasis alkenylation, alternative alkenylations, the Thorpe reaction, the Thorpe-Ziegler reaction, addition of silanes, formation of cyanohydrins, addition of HCN to C=N and C-N bonds, the Prins reaction, the benzoin condensation, addition of radicals to C=O, C=S, C=N compounds, the Ritter reaction, acylation of aldehydes and ketones, addition of aldehydes to aldehydes, the addition of isocyanates to isocyanates (formation of carbodiimides), the conversion of carboxylic acid salts to nitriles, the formation of epoxides from aldehydes and ketones, the formation of episulfides and episulfones, the formation of beta-lactones and oxetanes (e.g., the Paterno-Buchi reaction), the

formation of beta-lactams, etc. Reactions involving addition to isocyanides include the addition of water to isocyanides, the Passerini reaction, the Ug reaction, and the formation of metalated aldimines. Elimination reactions, including alpha, beta, and gamma eliminations, as well as extrusion reactions, can be performed using nucleotide-templated chemistry, although the strength of the reagents and conditions employed should be considered. Preferred elimination reactions include reactions that go by El, E2, ElcB, or E2C mechanisms. Exemplary reactions include, for example, reactions in which hydrogen is removed from one side (e.g., dehydration of alcohols, cleavage of ethers to alkenes, the Chugaev reaction, ester decomposition, cleavage of quarternary ammonium hydroxides, cleavage of quaternary ammonium salts with strong bases, cleavage of amine oxides, pyrolysis of keto-ylids, decomposition of toluene-p-sulfonylhydrazones, cleavage of sulfoxides, cleavage of selenoxides, cleavage of sulfornes, dehydrogalogenation of alkyl halides, dehydrohalogenation of acyl halides, dehydrohalogenation of sulfonyl halides, elimination of boranes, conversion of alkenes to alkynes, decarbonylation of acyl halides), reactions in which neither leaving atom is hydrogen (e.g., deoxygenation of vicinal diols, cleavage of cyclic thionocarbonates, conversion of epoxides to episulfides and alkenes, the Ramberg-Backlund reaction, conversion of aziridines to alkenes, dehalogenat[iota]on of vicinal dihalides, dehalogenation of alpha-halo acyl halides, and elimination of a halogen and a hetero group), fragmentation reactions (i.e., reactions in which carbon is the positive leaving group or the electrofuge, such as, for example, fragmentation of gamma-amino and gamma-hydroxy halides, fragmentation of 1,3- diols, decarboxylation of beta-hydroxy carboxylic acids, decarboxylation of (3-lactones, fragmentation of alpha-beta-epoxy hydrazones, elimination of CO from bridged bicydic compounds, and elimination Of CO2 from bridged bicydic compounds), reactions in which C=N or C=N bonds are formed (e.g., dehydration of aldoximes or similar compounds, conversion of ketoximes to nitriles, dehydration of unsubstituted amides, and conversion of I\l-alkylformamides to isocyanides), reactions in which C=O bonds are formed (e.g., pyrolysis of beta-hydroxy alkenes), and reactions in which N=N bonds are formed (e.g., eliminations to give diazoalkenes). Extrusion reactions include, for example, extrusion of N2 from pyrazolines, extrusion of N2 from pyrazoles, extrusion of N2 from triazolines, extrusion of CO, extrusion Of CO2, extrusion Of SO2, the Story synthesis, and alkene synthesis by twofold extrusion.

Rearrangements, including, for example, nudeophilic rearrangements, electrophilic rearrangements, prototropic rearrangements, and free-radical rearrangements, can also be performed using stage 1 and stage 2 synthesis schemes. Both 1,2 rearrangements and non-1,2 rearrangements can be performed. Exemplary reactions include, for example, carbon-to-carbon migrations of R, H, and Ar (e.g., Wagner-Meerwein and related reactions, the Pinacol rearrangement, ring expansion reactions, ring contraction reactions, acid-catalyzed rearrangements of aldehydes and ketones, the dienone-phenol rearrangement, the Favorskii rearrangement, the Arndt-Eistert synthesis, homologation of aldehydes, and homologation of ketones), carbon-to-carbon migrations of other groups (e.g., migrations of halogen, hydroxyl, amino, etc.; migration of boron; and the Neber rearrangement), carbon-to-nitrogen migrations of R and Ar (e.g., the Hofmann rearrangement, the Curtius rearrangement, the Lossen rearrangement, the Schmidt reaction, the Beckman rearrangement, the Stieglits rearrangement, and related rearrangements), carbon-to-oxygen migrations of R and Ar (e.g., the Baeyer-Villiger rearrangement and rearrangment of hydroperoxides), nitrogen-to-carbon, oxygen-to-carbon, and sulfur-to-carbon migration (e.g., the Stevens rearrangement, and the Wittig rearrangement), boron-to-carbon migrations (e.g., conversion of boranes to alcohols (primary or otherwise), conversion of boranes to aldehydes, conversion of boranes to carboxylic acids, conversion of vinylic boranes to alkenes, formation of alkynes from boranes and acetylides, formation of alkenes from boranes and acetylides, and formation of ketones from boranes and acetylides), electrocyclic rearrangements (e.g., of cydobutenes and 1,3-cyclohexadienes, or conversion of stilbenes to phenanthrenes), sigmatropic rearrangements (e.g., (1 ,j) sigmatropic migrations of hydrogen, (lj) sigmatropic migrations of carbon, conversion of vinylcydopropanes to cyclopentenes, the Cope rearrangement, the Claisen rearrangement, the Fischer indole synthesis, (2,3) sigmatropic rearrangements, and the benzidine rearrangement), other cyclic rearrangements (e.g., metathesis of alkenes, the di-n-methane and related rearrangements, and the Hofmann-Loffler and related reactions), and non-cyclic rearrangements (e.g., hydride shifts, the Chapman rearrangement, the Wallach rearrangement, and dybtropic rearrangements). Oxidative and reductive reactions may also be performed using stage 1 and stage 2 synthesis schemes. Exemplary reactions may involve, for example, direct electron transfer, hydride transfer, hydrogen-atom transfer, formation of ester intermediates, displacement mechanisms, or addition- elimination mechanisms. Exemplary oxidations include, for example, eliminations of hydrogen (e.g., aromatization of six-

membered rings, dehydrogenations yielding carbon-carbon double bonds, oxidation or dehydrogenation of alcohols to aldehydes and ketones, oxidation of phenols and aromatic amines to quinones, oxidative cleavage of ketones, oxidative cleavage of aldehydes, oxidative cleavage of alcohols, ozonolysis, oxidative cleavage of double bonds and aromatic rings, oxidation of aromatic side chains, oxidative decarboxylation, and bisdecarboxylation), reactions involving replacement of hydrogen by oxygen (e.g., oxidation of methylene to carbonyl, oxidation of methylene to OH, CO2R, or OR, oxidation of arylmethanes, oxidation of ethers to carboxylic esters and related reactions, oxidation of aromatic hydrocarbons to quinones, oxidation of amines or nitro compounds to aldehydes, ketones, or dihalides, oxidation of primary alcohols to carboxylic acids or carboxylic esters, oxidation of alkenes to aldehydes or ketones, oxidation of amines to nitroso compounds and hydroxylamines, oxidation of primary amines, oximes, azides, isocyanates, or nitroso compounds, to nitro compounds, oxidation of thiols and other sulfur compounds to sulfonic acids), reactions in which oxygen is added to the subtrate (e.g., oxidation of alkynes to alpha- diketones, oxidation of tertiary amines to amine oxides, oxidation of thioesters to sulfoxides and sulfones, and oxidation of carboxylic acids to peroxy acids, and oxidative coupling reactions (e.g., coupling involving carbanoins, dimerization of silyl enol ethers or of lithium enolates, and oxidation of thiols to disulfides).

Exemplary reductive reactions include, for example, reactions involving replacement of oxygen by hydrogen {e.g., reduction of carbonyl to methylene in aldehydes and ketones, reduction of carboxylic acids to alcohols, reduction of amides to amines, reduction of carboxylic esters to ethers, reduction of cyclic anhydrides to lactones and acid derivatives to alcohols, reduction of carboxylic esters to alcohols, reduction of carboxylic acids and esters to alkanes, complete reduction of epoxides, reduction of nitro compounds to amines, reduction of nitro compounds to hydroxylamines, reduction of nitroso compounds and hydroxylamines to amines, reduction of oximes to primary amines or aziridines, reduction of azides to primary amines, reduction of nitrogen compounds, and reduction of sulfonyl halides and sulfonic acids to thiols), removal of oxygen from the substrate {e.g., reduction of amine oxides and azoxy compounds, reduction of sulfoxides and sulfones, reduction of hydroperoxides and peroxides, and reduction of aliphatic nitro compounds to oximes or nitrites), reductions that include cleavage {e.g., de-alkylation of amines and amides, reduction of azo, azoxy, and hydrazo compounds to amines, and reduction of

disulfides to thiols), reductive coupling reactions {e.g., bimolecular reduction of aldehydes and ketones to 1,2-diols, bimolecular reduction of aldehydes or ketones to alkenes, acyloin ester condensation, reduction of nitro to azoxy compounds, and reduction of nitro to azo compounds), and. reductions in which an organic substrate is both oxidized and reduced {e.g., the Cannizzaro reaction, the Tishchenko reaction, the Pummerer rearrangement, and the Willgerodt reaction).

In one embodiment, a reactive group may comprise a nitrogen atom such as for example an amine, an isocyanate, an isocyanide, a hydroxylamine, a hydrazine, a nitrile, an amide, a lactam, an imine, an azo group, a nitro group, a nitroso group, an amidine group, a guanidine group, a carbamate, an azide, which may optionally be substituted by one or more substituents depending on the type of reactive group.
In one embodiment, a reactive group may comprise an oxygen atom such as for example a hydroxyl group, an ether, a ketone, an aldehyde, a hemiacetal, a hemiketal, an acetal, a ketal, a carboxylic acid, a carboxylic acid ester, an ortho ester, a carbonate, a carbamate, a lactam, a lactone, a hydroxyl amine, which may optionally be substituted by one or more substituents depending on the type of reactive group.
In one embodiment, a reactive group may comprise a sulfur atom such as for example a thiol, a disulfide, a sulfide, a sulfoxide, a sulfin amide, a sulfonamide, a sulfone, a sultam, a sultone, a thioketone, a thioaldehyde, a dithioacetal, a carboxylic acid thioester, a thiocarbonate, a thiocarbamate, a isothiocyanate, which may optionally be substituted by one or more substituents depending on the type of reactive group.
In one embodiment, a reactive group may comprise a halogen such as for example fluorine, chlorine, bromine, iodine, for example alkylchloride, alkylbromide, alkyliodide, alkenylchloride, alkenylbromide, alkenyliodide, alkynylchloride, alkynylbromide, alkynyliodide, arylfluoride, arylchloride, arylbromide, aryliodide, hetarylfluoride, hetarylchloride, hetarylbromide, hetaryliodide, carbonylfluoride, carbonylchloride, carbonylbromide, carbonyliodide, sulfonylfluoride, sulfonylchloride, sulfonylbromide, sulfonyliodide, which may optionally be substituted by one or more substituents depending on the type of reactive group.
In one embodiment, a reactive group may comprise a carbon atom such as for example an alkene, an alpha,beta-unsaturated ketone, an alpha,beta-unsaturated aldehyde, an alpha,beta-unsaturated carboxylic acid ester, an alpha,beta-unsaturated carboxylic acid amide, an alpha,beta-unsaturated sulfoxide, an

alpha,beta-unsaturated sulfone, an alpha,beta-unsaturated sulfonamide, an alpha,beta-unsaturated sulfonylchloride, a nitro alkene, such as a vinylogous nitro group (alpha,beta-unsaturated nitroalkene), an alkyne, an arene, a hetarene, a nitrile, an amide, a lactam, an imine, a nitroalkyl group, a nitroaryl group, an amidine group, a carbamate, a ketone, an aldehyde, a hemiacetal, a hemiketal, an acetal, a ketal, a carboxylic acid, a carboxylic acid ester, an ortho ester, a carbonate, a carbamate, a lactam, a lactone, a carbosulfone, a carbosultam, a carbosultone, a thioketone, a thioaldehyde, a dithioacetal, a carboxylic acid thioester, a thiocarbonate, a thiocarbamate, an alkylchloride, an alkylbromide, an alkyliodide, an alkenylchloride, an alkenylbromide, an alkenyliodide, an alkynylchloride, an alkynylbromide, an alkynyliodide, an arylfluoride, an arylchloride, an arylbromide, an aryliodide, an hetarylfluoride, an hetarylchloride, an hetarylbromide, an hetaryliodide, an carbonylfluoride, an carbonylchloride, an carbonylbromide, an carbonyliodide, an isocyanate, an isothiocyanate, an isocyanide, a alkylphosphonium group such as for example alkyltriphenylphosphonium chloride, for example alkyltriphenylphosphonium bromide, for example alkyltriphenylphosphonium iodide, which may optionally be substituted by one or more substituents depending on the type of reactive group.

Reactive groups may also comprising further functional groups as described in Comprehensive Organic Functional Group Transformations, Eds. A.R. Katritsky, O. Meth-Cohn, C.W. Rees, Pergamon, Elsevier 1995 Volumes 1-6, which are hereby incorporated by reference.

A chemical reactive site may comprise one or more reactive groups for example chemical reactive sites comprising 1-10 reactive groups, for example one reactive group, for example two reactive groups, for example three reactive groups, for example four reactive groups, for example five reactive groups.
A reactant may comprise one or more reactive groups for example reactants comprising 1-10 reactive groups, for example one reactive group, for example two reactive groups, for example three reactive groups, for example four reactive groups, for example five reactive groups.

In one embodiment, a reactant comprises two reactive groups, such as for example a diamine, an aminoketone, an aminoalcohol, an aminothiol, an aminoacid, such as for example an amino carboxylic acid, an aminoacid ester such as for example and

amino carboxylic acid ester, an aminoacid amide such as for example an amino carboxylic acid amide, an amino chloroazine such as for example an amino chloropyridine, for example an amino chloropyrimidine, an amino chloropyridazine, an amino chloropyrazine, an amino fluoroazine such as for example an amino fluoropyridin, for example an amino fluoropyrimidine, an amino fluoropyridazine, an amino fluoro pyrazine, an Fmoc protected diamine, an Fmoc protected aminoketone, an Fmoc protected aminoalcohol, an Fmoc protected aminoacid such as for example an Fmoc protected amino carboxylic acid, an Fmoc protected aminoacid ester such as for example an Fmoc protected amino carboxylic acid ester, an Fmoc protected aminoacid amide such as for example an Fmoc protected amino carboxylic acid amide, an Fmoc protected aminoisocyanate, an Fmoc protected amino chloroazine such as for example an Fmoc protected amino chloropyridine, for example an Fmoc protected amino chloropyrimidine, an Fmoc protected amino chloropyridazine, an Fmoc protected amino chloropyrazine, an Fmoc protected amino fluoroazine such as for example an Fmoc protected amino fluoropyridin, for example an Fmoc protected amino fluoropyrimidine, an Fmoc protected amino fluoropyridazine, an Fmoc protected amino fluoro pyrazine, an Fmoc protected aminosulfonylchloride, an Fmoc protected aminoaldehyde, an Fmoc protected aminoisocyanate, an MSc protected diamine, an MSc protected aminoketone, an MSc protected aminoalcohol, an MSc protected aminoacid, an MSc protected aminoacid such as for example an MSc protected amino carboxylic acid, an MSc protected aminoacid ester such as for example an MSc protected amino carboxylic acid ester, an MSc protected aminoacid amide such as for example an MSc protected amino carboxylic acid amide, an MSc protected aminoisocyanate, an MSc protected amino chloroazine such as for example an MSc protected amino chloropyridine, for example an MSc protected amino chloropyrimidine, an MSc protected amino chloropyridazine, an MSc protected amino chloropyrazine, an MSc protected amino fluoroazine such as for example an MSc protected amino fluoropyridin, for example an MSc protected amino fluoropyrimidine, an MSc protected amino fluoropyridazine, an MSc protected amino fluoro pyrazine, an MSc protected aminosulfonylchloride, an MSc protected aminoaldehyde, an MSc protected aminoisocyanate, a 4-pentenoyl protected diamine, a 4-pentenoyl protected aminoketone, a 4-pentenoyl protected aminoalcohol, a 4-pentenoyl protected aminoacid such as for example a 4-pentenoyl protected amino carboxylic acid, a 4-pentenoyl protected aminoacid ester such as for example a 4-pentenoyl protected amino carboxylic acid ester, a 4-pentenoyl

protected aminoacid amide such as for example a 4-pentenoyl protected amino carboxylic acid amide, a 4-pentenoyl protected aminoisocyanate, a 4-pentenoyl protected amino chloroazine such as for example a 4-pentenoyl protected amino chloropyridine, for example an 4-pentenoyl protected amino chloropyrimidine, a 4-pentenoyl protected amino chloropyridazine, a 4-pentenoyl protected amino chloropyrazine, a 4-pentenoyl protected amino fluoroazine such as for example a 4-pentenoyl protected amino fluoropyridin, for example a 4-pentenoyl protected amino fluoropyrimidine, a 4-pentenoyl protected amino fluoropyridazine, a 4-pentenoyl protected amino fluoro pyrazine, a 4-pentenoyl protected aminosulfonylchloride, a 4-pentenoyl protected aminoaldehyde, a 4-pentenoyl protected aminoisocyanate, a Boc protected diamine, a Boc protected aminoketone, a Boc protected aminoalcohol, a Boc protected aminoacid such as for example a Boc protected amino carboxylic acid, a Boc protected aminoacid ester such as for example a Boc protected amino carboxylic acid ester, a Boc protected aminoacid amide such as for example a Boc protected amino carboxylic acid amide, a Boc protected aminoisocyanate, a Boc protected amino chloroazine such as for example an Boc protected amino chloropyridine, for example a Boc protected amino chloropyrimidine, a Boc protected amino chloropyridazine, a Boc protected amino chloropyrazine, a Boc protected amino fluoroazine such as for example a Boc protected amino fluoropyridin, for example an Boc protected amino fluoropyrimidine, an Boc protected amino fluoropyridazine, an Boc protected amino fluoro pyrazine, a o-Ns protected diamine, a o-Ns protected aminoketone, a o-Ns protected aminoalcohol, a o-Ns protected aminoacid such as for example a o-Ns protected amino carboxylic acid, a o-Ns protected aminoacid ester such as for example a o-Ns protected amino carboxylic acid ester, a o-Ns protected aminoacid amide such as for example a o-Ns protected amino carboxylic acid amide, a o-Ns protected aminoisocyanate, a o-Ns protected amino chloroazine such as for example an o-Ns protected amino chloropyridine, for example a o-Ns protected amino chloropyrimidine, a o-Ns protected amino chloropyridazine, a o-Ns protected amino chloropyrazine, a o-Ns protected amino fluoroazine such as for example a o-Ns protected amino fluoropyridin, for example an o-Ns protected amino fluoropyrimidine, an o-Ns protected amino fluoropyridazine, an o-Ns protected amino fluoro pyrazine, a p-Ns protected diamine, a p-Ns protected aminoketone, a p-Ns protected aminoalcohol, a p-Ns protected aminoacid such as for example a p-Ns protected amino carboxylic acid, a p-Ns protected aminoacid ester such as for example a p-Ns protected amino carboxylic acid ester, a p-Ns protected aminoacid

amide such as for example a p-Ns protected amino carboxylic acid amide, a p-Ns protected aminoisocyanate, a p-Ns protected amino chloroazine such as for example an p-Ns protected amino chloropyridine, for example a p-Ns protected amino chloropyrimidine, a p-Ns protected amino chloropyridazine, a p-Ns protected amino chloropyrazine, a p-Ns protected amino fluoroazine such as for example a p-Ns protected amino fluoropyridin, for example an p-Ns protected amino fluoropyrimidine, an p-Ns protected amino fluoropyridazine, an p-Ns protected amino fluoro pyrazine, a allyl carbamate protected diamine, a allyl carbamate protected aminoketone, a allyl carbamate protected aminoalcohol, a allyl carbamate protected aminoacid such as for example a allyl carbamate protected amino carboxylic acid, a allyl carbamate protected aminoacid ester such as for example a allyl carbamate protected amino carboxylic acid ester, a allyl carbamate protected aminoacid amide such as for example a allyl carbamate protected amino carboxylic acid amide, a allyl carbamate protected aminoisocyanate, a allyl carbamate protected amino chloroazine such as for example an allyl carbamate protected amino chloropyridine, for example a allyl carbamate protected amino chloropyrimidine, a allyl carbamate protected amino chloropyridazine, a allyl carbamate protected amino chloropyrazine, a allyl carbamate protected amino fluoroazine such as for example a allyl carbamate protected amino fluoropyridin, for example an allyl carbamate protected amino fluoropyrimidine, an allyl carbamate protected amino fluoropyridazine, an allyl carbamate protected amino fluoro pyrazine, a benzyl carbamate protected diamine, a benzyl carbamate protected aminoketone, a benzyl carbamate protected aminoalcohol, a benzyl carbamate protected aminoacid such as for example a benzyl carbamate protected amino carboxylic acid, a benzyl carbamate protected aminoacid ester such as for example a benzyl carbamate protected amino carboxylic acid ester, a benzyl carbamate protected aminoacid amide such as for example a benzyl carbamate protected amino carboxylic acid amide, a benzyl carbamate protected aminoisocyanate, a benzyl carbamate protected amino chloroazine such as for example an benzyl carbamate protected amino chloropyridine, for example a benzyl carbamate protected amino chloropyrimidine, a benzyl carbamate protected amino chloropyridazine, a benzyl carbamate protected amino chloropyrazine, a benzyl carbamate protected amino fluoroazine such as for example a benzyl carbamate protected amino fluoropyridin, for example an benzyl carbamate protected amino fluoropyrimidine, an benzyl carbamate protected amino fluoropyridazine, an benzyl carbamate protected amino fluoro pyrazine, a Fmoc protected aminofluorotriazine

such as for example a Fmoc protected aminofluoro-1,2,3-triazine, for example a Fmoc protected aminofluoro-1,2,4-triazine, for example a a Fmoc protected aminofluoro-1,3,5-triazine, a Fmoc protected aminochlorotriazine such as for example a Fmoc protected aminochloro-1,2,3-triazine, for example a Fmoc protected aminochloro-1,2,4-triazine, for example a a Fmoc protected aminochloro-1,3,5-triazine, a MSc protected aminofluorotriazine such as for example a MSc protected aminofluoro-1,2,3-triazine, for example a MSc protected aminofluoro-1,2,4-triazine, for example a a MSc protected aminofluoro-1,3,5-triazine, a MSc protected aminochlorotriazine such as for example a MSc protected aminochloro-1,2,3-triazine, for example a MSc protected aminochloro-1,2,4-triazine, for example a a MSc protected aminochloro-1,3,5-triazine, a o-Ns protected aminofluorotriazine such as for example a o-Ns protected aminofluoro-1,2,3-triazine, for example a o-Ns protected aminofluoro-1,2,4-triazine, for example a a o-Ns protected aminofluoro-1,3,5-triazine, a o-Ns protected aminochlorotriazine such as for example a o-Ns protected aminochloro-1,2,3-triazine, for example a o-Ns protected aminochloro-1,2,4-triazine, for example a a o-Ns protected aminochloro-1,3,5-triazine, a p-Ns protected aminofluorotriazine such as for example a p-Ns protected aminofluoro-1,2,3-triazine, for example a p-Ns protected aminofluoro-1,2,4-triazine, for example a a p-Ns protected aminofluoro-1,3,5-triazine, a p-Ns protected aminochlorotriazine such as for example a p-Ns protected aminochloro-1,2,3-triazine, for example a p-Ns protected aminochloro-1,2,4-triazine, for example a a p-Ns protected aminochloro-1,3,5-triazine, a allyl carbamate protected aminofluorotriazine such as for example a allyl carbamate protected aminofluoro-1,2,3-triazine, for example a allyl carbamate protected aminofluoro-1,2,4-triazine, for example a a allyl carbamate protected aminofluoro-1,3,5-triazine, a allyl carbamate protected aminochlorotriazine such as for example a allyl carbamate protected aminochloro-1,2,3-triazine, for example a allyl carbamate protected aminochloro-1,2,4-triazine, for example a a allyl carbamate protected aminochloro-1,3,5-triazine, a benzyl carbamate protected aminofluorotriazine such as for example a benzyl carbamate protected aminofluoro-1,2,3-triazine, for example a benzyl carbamate protected aminofluoro-1,2,4-triazine, for example a a benzyl carbamate protected aminofluoro-1,3,5-triazine, a benzyl carbamate protected aminochlorotriazine such as for example a benzyl carbamate protected aminochloro-1,2,3-triazine, for example a benzyl carbamate protected aminochloro-1,2,4-triazine, for example a a benzyl carbamate protected aminochloro-1,3,5-triazine, wherein such reactive groups may optionally be protected by protection groups, for example amino protection groups such as for

example Fmoc, for example MSc, for example Boc, for example 4-pentenoyl, for example o-Ns, for example p-Ns, for example allyl carbamate, for example benzyl carbamate and a combination thereof, for example carboxylic acid protection such as methyl ester, ethyl ester, t-butyl ester, 2,2,2-trichloroethyl ester, benzyl ester, p-methoxy benzyl ester, o-nitrobenzyl ester, methylsulfonylethyl ester, for example aldehyde protection such as an acetal or the aldehyde may optionally be masked as a 1,2-diol and a combination thereof, wherein such reactants may optionally be substituted by one or more substituents.

In a further embodiment, a reactant comprises two reactive groups, such as for example a mercaptoaldehyde, a hydroxyaldehyde, a formylalkyl carboxylic acid, a formyl aryl carboxylic acid, a formyl hetaryl carboxylic acid, a formyl alkylaryl carboxylic acid, a formyl alkylhetaryl carboxylic acid, a formyl arylalkyl carboxylic acid, a formyl hetarylalkyl carboxylic acid, a formylalkyl carboxylic acid ester, a formyl aryl carboxylic acid ester, a formyl hetaryl carboxylic acid ester, a formyl alkylaryl carboxylic acid ester, a formyl alkylhetaryl carboxylic acid ester, a formyl arylalkyl carboxylic acid ester, a formyl hetarylalkyl carboxylic acid ester, a formylalkyl sulfonyl chloride, a formyl aryl sulfonyl chloride, a formyl hetaryl sulfonyl chloride, a formyl alkylaryl sulfonyl chloride, a formyl alkylhetaryl sulfonyl chloride, a formyl arylalkyl sulfonyl chloride, a formyl hetarylalkyl sulfonyl chloride, a formylalkyl isocyanate, a formyl aryl isocyanate, a formyl hetaryl isocyanate, a formyl alkylaryl isocyanate, a formyl alkylhetaryl isocyanate, a formyl arylalkyl isocyanate, a formyl hetarylalkyl isocyanate, a formylalkyl isocyanide, a formyl aryl isocyanide, a formyl hetaryl isocyanide, a formyl alkylaryl isocyanide, a formyl alkylhetaryl isocyanide, a formyl arylalkyl isocyanide, a formyl hetarylalkyl isocyanide, a formyl chloroazine such as for example a formyl chloropyridine, for example a formyl chloropyrimidine, a formyl chloropyridazine, a formyl chloropyrazine, a formyl fluoroazine such as for example a formyl fluoropyridin, for example a formyl fluoropyrimidine, a formyl fluoropyridazine, a formyl fluoro pyrazine, a formyl fluorotriazine, a formylchlorotriazine, wherein such reactive groups may optionally be protected by protection groups, for example amino protection groups such as for example Fmoc, for example MSc, for example Boc, for example 4-pentenoyl, for example o-Ns, for example p-Ns, for example allyl carbamate, for example benzyl carbamate and a combination thereof, for example carboxylic acid protection such as methyl ester, ethyl ester, t-butyl ester, 2,2,2-trichloroethyl ester, benzyl ester, p-methoxy benzyl ester, o-nitrobenzyl ester, methylsulfonylethyl ester, for example aldehyde protection

such as an acetal or the aldehyde may optionally be masked as a 1,2-diol and a combination thereof, wherein such reactants may optionally be substituted by one or more substituents.

In a further embodiment, a reactant comprises two reactive groups, such as for example a dicarboxylic acid, a alkoxycarbonylalkyl carboxylic acid, a alkoxycarbonyl aryl carboxylic acid, a alkoxycarbonyl hetaryl carboxylic acid, a alkoxycarbonyl alkylaryl carboxylic acid, a alkoxycarbonyl alkylhetaryl carboxylic acid, a alkoxycarbonyl arylalkyl carboxylic acid, a alkoxycarbonyl hetarylalkyl carboxylic acid, a carboxyalkyl sulfonyl chloride, a carboxy aryl sulfonyl chloride, a carboxy hetaryl sulfonyl chloride, a carboxy alkylaryl sulfonyl chloride, a carboxy alkylhetaryl sulfonyl chloride, a carboxy arylalkyl sulfonyl chloride, a carboxy hetarylalkyl sulfonyl chloride, a alkoxycarbonylalkyl sulfonyl chloride, a alkoxycarbonyl aryl sulfonyl chloride, a alkoxycarbonyl hetaryl sulfonyl chloride, a alkoxycarbonyl alkylaryl sulfonyl chloride, a alkoxycarbonyl alkylhetaryl sulfonyl chloride, a alkoxycarbonyl arylalkyl sulfonyl chloride, a alkoxycarbonyl hetarylalkyl sulfonyl chloride, a alkoxycarbonylalkyl isocyanate, a alkoxycarbonyl aryl isocyanate, a alkoxycarbonyl hetaryl isocyanate, a alkoxycarbonyl alkylaryl isocyanate, a alkoxycarbonyl alkylhetaryl isocyanate, a alkoxycarbonyl arylalkyl isocyanate, a alkoxycarbonyl hetarylalkyl isocyanate, a alkoxycarbonyl chloroazine such as for example a alkoxycarbonyl chloropyridine, for example a alkoxycarbonyl chloropyrimidine, a alkoxycarbonyl chloropyridazine, a alkoxycarbonyl chloropyrazine, a alkoxycarbonyl fluoroazine such as for example a alkoxycarbonyl fluoropyridin, for example a alkoxycarbonyl fluoropyrimidine, a alkoxycarbonyl fluoropyridazine, a alkoxycarbonyl fluoro pyrazine, a alkoxycarbonyl fluorotriazine, a alkoxycarbonylchlorotriazine, a carboxycarbonyl chloroazine such as for example a carboxycarbonyl chloropyridine, for example a carboxycarbonyl chloropyrimidine, a carboxycarbonyl chloropyridazine, a carboxycarbonyl chloropyrazine, a carboxycarbonyl fluoroazine such as for example a carboxycarbonyl fluoropyridin, for example a carboxycarbonyl fluoropyrimidine, a carboxycarbonyl fluoropyridazine, a carboxycarbonyl fluoro pyrazine, a carboxycarbonyl fluorotriazine, a carboxycarbonylchlorotriazine, a chlorosulfonyl chloroazine such as for example a chlorosulfonyl chloropyridine, for example a chlorosulfonyl chloropyrimidine, a chlorosulfonyl chloropyridazine, a chlorosulfonyl chloropyrazine, a chlorosulfonyl fluoroazine such as for example a chlorosulfonyl fluoropyridin, for example a chlorosulfonyl fluoropyrimidine, a chlorosulfonyl fluoropyridazine, a chlorosulfonyl fluoro pyrazine, a chlorosulfonyl

fluorotriazine, a chlorosulfonylchlorotriazine, a dihaloazine such as for example a dihalopyridin, for example a dihalopyrimidine, a dihalopyridazine, a dihalo pyrazine, a dihalotriazine, a dihalotriazine such as for example a dihalo-1,2,3-triazine, for example a dihalo-1,2,4-triazine, for example a dihalo-1,3,5-triazine, a dichloroazine such as for example a dichloropyridin, for example a dichloropyrimidine, a dichloropyridazine, a dichloro pyrazine, a dichlorotriazine, a dichlorotriazine such as for example a dichloro-1,2,3-triazine, for example a dichloro-1,2,4-triazine, for example a dichloro-1,3,5-triazine, a difluoroazine such as for example a difluoropyridin, for example a difluoropyrimidine, a difluoropyridazine, a difluoro pyrazine, a difluorotriazine, a difluorotriazine such as for example a difluoro-1,2,3-triazine, for example a difluoro-1,2,4-triazine, for example a difluoro-1,3,5-triazine, a chlorofluoroazine such as for example a chlorofluoropyridin, for example a chlorofluoropyrimidine, a chlorofluoropyridazine, a chlorofluoro pyrazine, a chlorofluorotriazine, a chlorofluorotriazine such as for example a chlorofluoro-1,2,3-triazine, for example a chlorofluoro-1,2,4-triazine, for example a chlorofluoro-1,3,5-triazine, wherein such reactive groups may optionally be protected by further protection groups, for example carboxylic acid protection such as methyl ester, ethyl ester, t-butyl ester, 2,2,2-trichloroethyl ester, methylsulfonylethyl ester, benzyl ester, p-methoxy benzyl ester, o-nitrobenzyl ester, wherein such reactive groups may optionally be protected by protection groups, for example amino protection groups such as for example Fmoc, for example MSc, for example Boc, for example 4-pentenoyl, for example o-Ns, for example p-Ns, for example allyl carbamate, for example benzyl carbamate and a combination thereof, for example carboxylic acid protection such as methyl ester, ethyl ester, t-butyl ester, 2,2,2-trichloroethyl ester, benzyl ester, p-methoxy benzyl ester, o-nitrobenzyl ester, methylsulfonylethyl ester, for example aldehyde protection such as an acetal or the aldehyde may optionally be masked as a 1,2-diol and a combination thereof, wherein such reactants may optionally be substituted by one or more substituents.

In a further embodiment, a reactant comprises two reactive groups, such as for example an alpha,beta-unsaturated aldehyde, an alpha,beta-unsaturated sulfonyl chloride, an alpha,beta-unsaturated carboxylic acid, an alpha,beta-unsaturated carboxylic acid ester, an alpha,beta-unsaturated isocyanate, an alpha,beta-unsaturated ketone, wherein such reactive groups may optionally be protected by protection groups, for example amino protection groups such as for example Fmoc, for example MSc, for example Boc, for example 4-pentenoyl, for example o-Ns, for

example p-Ns, for example allyl carbamate, for example benzyl carbamate and a combination thereof, for example carboxylic acid protection such as methyl ester, ethyl ester, t-butyl ester, 2,2,2-trichloroethyl ester, benzyl ester, p-methoxy benzyl ester, o-nitrobenzyl ester, methylsulfonylethyl ester, for example aldehyde protection such as an acetal or the aldehyde may optionally be masked as a 1,2-diol and a combination thereof, wherein such reactants may optionally be substituted by one or more substituents.

In a further embodiment, a reactant comprises three reactive groups, such as for example a triamine, a diamino carboxylic acid, an amino dicarboxylic acid, a tricarboxylic acid, wherein such reactive groups may optionally be protected by protection groups, for example amino protection groups such as for example Fmoc, for example MSc, for example Boc, for example 4-pentenoyl, for example o-Ns, for example p-Ns, for example allyl carbamate, for example benzyl carbamate and a combination thereof, for example carboxylic acid protection such as methyl ester, ethyl ester, t-butyl ester, 2,2,2-trichloroethyl ester, benzyl ester, p-methoxy benzyl ester, o-nitrobenzyl ester, methylsulfonylethyl ester, for example aldehyde protection such as an acetal or the aldehyde may optionally be masked as a 1,2-diol and a combination thereof, wherein such reactants may optionally be substituted by one or more substituents.

In a further embodiment, a reactant comprises three reactive groups, such as for example trihalotriazine for example trichlorotriazine, trifluorotriazine, dichlorofluorotriazine, difluorochlorotriazine, such as for example formyl dihaloazines, carboxy dihaloazines, chlorosulfonyl dihaloazines, isocyanato dihaloazines, amino dihaloazines, trihaloazinylazine, dihaloazinylhaloazine, wherein such reactive groups may optionally be protected by protection groups, for example amino protection groups such as for example Fmoc, for example MSc, for example Boc, for example 4-pentenoyl, for example o-Ns, for example p-Ns, for example allyl carbamate, for example benzyl carbamate and a combination thereof, for example carboxylic acid protection such as methyl ester, ethyl ester, t-butyl ester, 2,2,2-trichloroethyl ester, benzyl ester, p-methoxy benzyl ester, o-nitrobenzyl ester, methylsulfonylethyl ester, for example aldehyde protection such as an acetal or the aldehyde may optionally be masked as a 1,2-diol and a combination thereof, wherein such reactants may optionally be substituted by one or more substituents.

In a further embodiment, a reactant comprises three reactive groups, such as for example a diamino aldehyde, an amino dialdehyde, a trialdehyde, wherein such reactive groups may optionally be protected by protection groups, for example amino protection groups such as for example Fmoc, for example MSc, for example Boc, for example 4-pentenoyl, for example o-Ns, for example p-Ns, for example allyl carbamate, for example benzyl carbamate and a combination thereof, for example carboxylic acid protection such as methyl ester, ethyl ester, t-butyl ester, 2,2,2-trichloroethyl ester, benzyl ester, p-methoxy benzyl ester, o-nitrobenzyl ester, methylsulfonylethyl ester, for example aldehyde protection such as an acetal or the aldehyde may optionally be masked as a 1,2-diol and a combination thereof, wherein such reactants may optionally be substituted by one or more substituents.

In a further embodiment, a reactant comprises three reactive groups, such as for example a diformyl carboxylic acid, a formyl dicarboxylic acid, a formyl amino carboxylic acid, wherein such reactive groups may optionally be protected by protection groups, for example amino protection groups such as for example Fmoc, for example MSc, for example Boc, for example 4-pentenoyl, for example o-Ns, for example p-Ns, for example allyl carbamate, for example benzyl carbamate and a combination thereof, for example carboxylic acid protection such as methyl ester, ethyl ester, t-butyl ester, 2,2,2-trichloroethyl ester, benzyl ester, p-methoxy benzyl ester, o-nitrobenzyl ester, methylsulfonylethyl ester, for example aldehyde protection such as an acetal or the aldehyde may optionally be masked as a 1,2-diol and a combination thereof, wherein such reactants may optionally be substituted by one or more substituents.

In a further embodiment, a reactant comprises three reactive groups, such as for example an alpha,beta-unsaturated aminoaldehyde, an alpha,beta-unsaturated aminosulfonyl chloride, an alpha,beta-unsaturated aminocarboxylic acid, an alpha,beta-unsaturated aminocarboxylic acid ester, an alpha,beta-unsaturated aminoisocyanate, an alpha,beta-unsaturated aminoketone, an alpha,beta-unsaturated aminocarboxylic acid amide, an alpha,beta-unsaturated aminosulfoxide, an alpha,beta-unsaturated aminosulfone, an alpha,beta-unsaturated aminosulfonamide, an alpha,beta-unsaturated aminosulfonylchloride, a nitro aminoalkene, such as comprising a vinylogous nitro group (alpha,beta-unsaturated nitroaminoalkene), an alpha,beta-unsaturated formylaldehyde, an alpha,beta-unsaturated formylsulfonyl chloride, an alpha,beta-unsaturated formylcarboxylic

acid, an alpha,beta-unsaturated formylcarboxylic acid ester, an alpha,beta-unsaturated formylisocyanate, an alpha,beta-unsaturated formylketone, an alpha,beta-unsaturated formylcarboxylic acid amide, an alpha,beta-unsaturated formylsulfoxide, an alpha,beta-unsaturated formylsulfone, an alpha,beta-unsaturated formylsulfonamide, an alpha,beta-unsaturated formylsulfonylchloride, a nitro formylalkene, such as comprising a vinylogous nitro group (alpha,beta-unsaturated nitroformylalkene), wherein such reactive groups may optionally be protected by protection groups, for example amino protection groups such as for example Fmoc, for example MSc, for example Boc, for example 4-pentenoyl, for example o-Ns, for example p-Ns, for example allyl carbamate, for example benzyl carbamate and a combination thereof, for example carboxylic acid protection such as methyl ester, ethyl ester, t-butyl ester, 2,2,2-trichloroethyl ester, benzyl ester, p-methoxy benzyl ester, o-nitrobenzyl ester, methylsulfonylethyl ester, for example aldehyde protection such as an acetal or the aldehyde may optionally be masked as a 1,2-diol and a combination thereof, wherein such reactants may optionally be substituted by one or more substituents.

In a further embodiment, a reactant comprises three reactive groups, such as for example an alpha,beta-unsaturated carboxyaldehyde, an alpha,beta-unsaturated carboxysulfonyl chloride, an alpha,beta-unsaturated carboxycarboxylic acid, an alpha,beta-unsaturated carboxycarboxylic acid ester, an alpha,beta-unsaturated carboxyisocyanate, an alpha,beta-unsaturated carboxyketone, wherein such reactive groups may optionally be protected by protection groups, for example amino protection groups such as for example Fmoc, for example MSc, for example Boc, for example 4-pentenoyl, for example o-Ns, for example p-Ns, for example allyl carbamate, for example benzyl carbamate and a combination thereof, for example carboxylic acid protection such as methyl ester, ethyl ester, t-butyl ester, 2,2,2-trichloroethyl ester, benzyl ester, p-methoxy benzyl ester, o-nitrobenzyl ester, methylsulfonylethyl ester, for example aldehyde protection such as an acetal or the aldehyde may optionally be masked as a 1,2-diol and a combination thereof, wherein such reactants may optionally be substituted by one or more substituents.

In a further embodiment, a reactant comprises three reactive groups, such as for example an alpha,beta-unsaturated alkoxycarbonylaldehyde, an alpha,beta-unsaturated alkoxycarbonylsulfonyl chloride, an alpha,beta-unsaturated alkoxycarbonylcarboxylic acid, an alpha,beta-unsaturated alkoxycarbonylcarboxylic

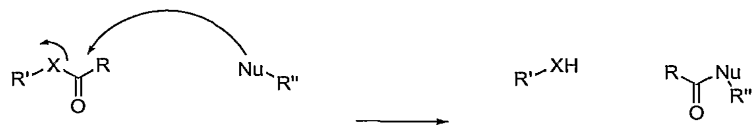
acid ester, an alpha,beta-unsaturated alkoxycarbonylisocyanate, an alpha,beta-unsaturated alkoxycarbonylketone, wherein such reactive groups may optionally be protected by protection groups, for example amino protection groups such as for example Fmoc, for example MSc, for example Boc, for example 4-pentenoyl, for example o-Ns, for example p-Ns, for example allyl carbamate, for example benzyl carbamate and a combination thereof, for example carboxylic acid protection such as methyl ester, ethyl ester, t-butyl ester, 2,2,2-trichloroethyl ester, benzyl ester, p-methoxy benzyl ester, o-nitrobenzyl ester, methylsulfonylethyl ester, for example aldehyde protection such as an acetal or the aldehyde may optionally be masked as a 1,2-diol and a combination thereof, wherein such reactants may optionally be substituted by one or more substituents.

In a further embodiment, a reactant comprises three reactive groups, such as for example an alpha,beta-unsaturated formylaldehyde, an alpha,beta-unsaturated formylsulfonyl chloride, an alpha,beta-unsaturated formylcarboxylic acid, an alpha,beta-unsaturated formylcarboxylic acid ester, an alpha,beta-unsaturated formylisocyanate, an alpha,beta-unsaturated formylketone, wherein such reactive groups may optionally be protected by protection groups, for example amino protection groups such as for example Fmoc, for example MSc, for example Boc, for example 4-pentenoyl, for example o-Ns, for example p-Ns, for example allyl carbamate, for example benzyl carbamate and a combination thereof, for example carboxylic acid protection such as methyl ester, ethyl ester, t-butyl ester, 2,2,2-trichloroethyl ester, benzyl ester, p-methoxy benzyl ester, o-nitrobenzyl ester, methylsulfonylethyl ester, for example aldehyde protection such as an acetal or the aldehyde may optionally be masked as a 1,2-diol and a combination thereof, wherein such reactants may optionally be substituted by one or more substituents.

Further reactive group reactions are illustrated herein below. The illustrations should not be construed as limiting the scope of the present invention in any way.

Nucleophilic substitution using activation of electrophiles

A. Acylating monomer building blocks (reactants) - principle



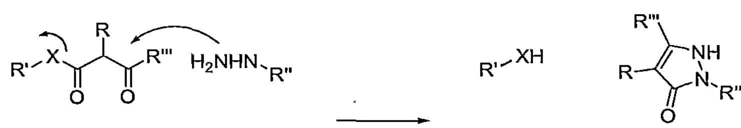
X = O , S Nu = Oxygen- , Nitrogen- , Sulfur- and Carbon Nucleophiles

B. Acylation

Amide formation by reaction of amines with activated esters

C. Acylation

Pyrazolone formation by reaction of hydrazines with alpha-ketoesters

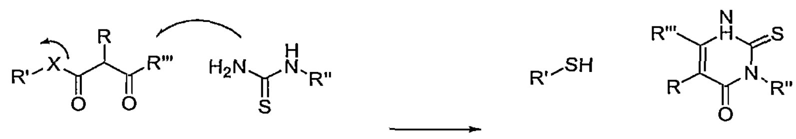


D. Acylation

Isoxazolone formation by reaction of hydroxylamines with alpha-ketoesters

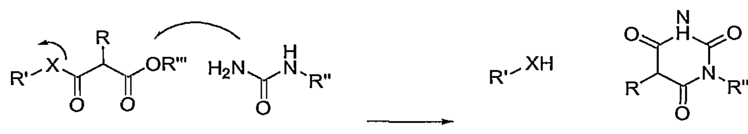
E. Acylation

Pyrimidine formation by reaction of thioureas with alpha-ketoesters



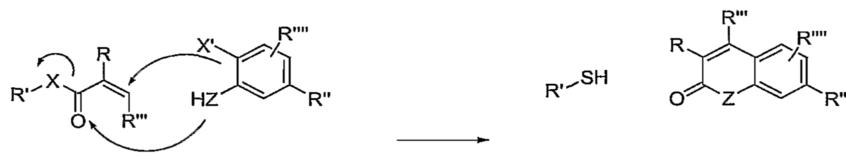
F. Acylation

Pyrimidine formation by reaction of ureas with Malonates



G. Acylation

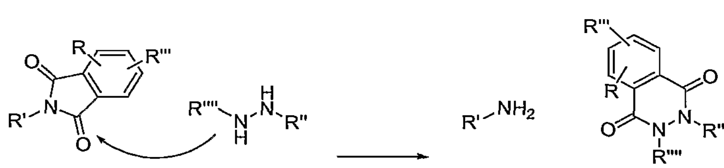
Coumarine or quinolinon formation by a Heck reaction followed by a nucleophilic substitution



X = O,S X' = Halogen, OTf, OMs Z = O, NH

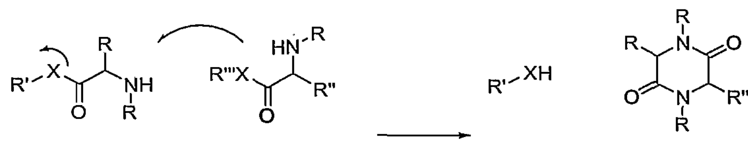
H. Acylation

Phthalhydrazide formation by reaction of Hydrazines and Phthalimides



I. Acylation

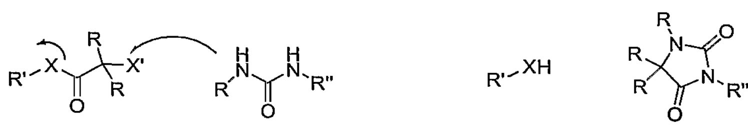
Diketopiperazine formation by reaction of Amino Acid Esters



X = O, S R' = H, R

J. Acylation

Hydantoin formation by reaction of Urea and α-substituted Esters



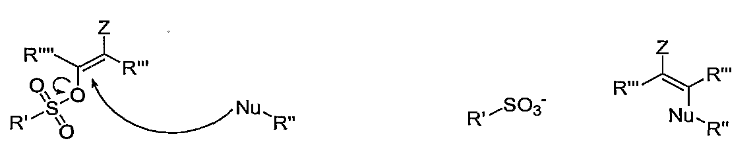
X = O, S X' = Hal, OTos, OMs, etc.

K. Alkylating monomer building blocks (reactants) - principle

Alkylated compounds by reaction of Sulfonates with Nucleofiles

Nu = Oxygen- , Nitrogen- , Sulfur- and Carbon Nucleophiles

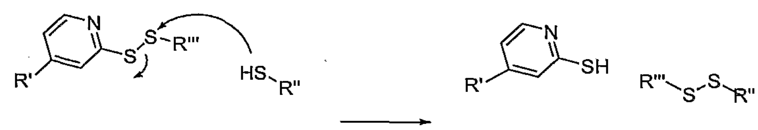
L. Vinylating monomer building blocks (reactants) - principle



Z = CN, COOR, COR, NO_2, SO_2R, S(=O)R, SO_2NR_2, F
Nu = Oxygen- , Nitrogen- , Sulfur- and Carbon Nucleophiles

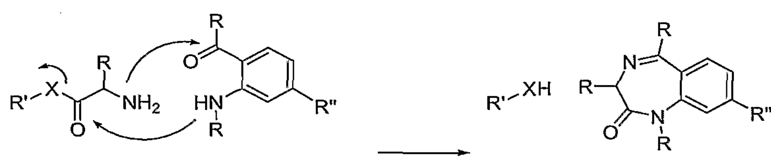
M. Heteroatom electrophiles

Disulfide formation by reaction of Pyridyl disulfide with Mercaptanes



N. Acylation

Benzodiazepinone formation by reaction of Amino Acid Esters and Amino Ketones

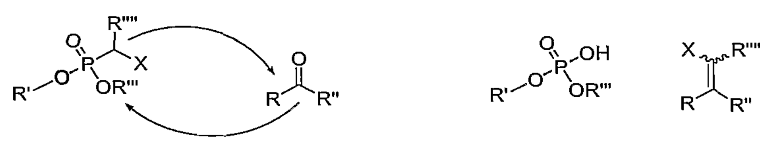


X = O, S

Addition to carbon-hetero multiple bonds:

O. Wittig/Horner-Wittig-Emmons reagents

Substituted alkene formation by reaction of Phosphonates with Aldehydes or Ketones

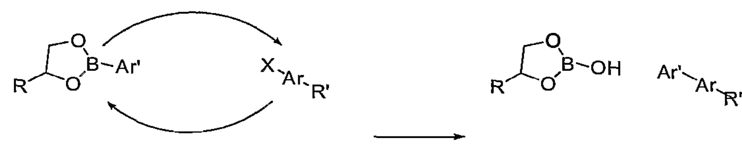


X = EWG

Transition metal catalysed reactions

P. Arylation

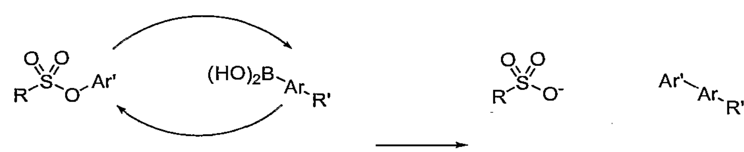
Biaryl formation by the reaction of Boronates with Aryls or Heteroaryls



X = Halogen, OMs, OTf, OTos, etc

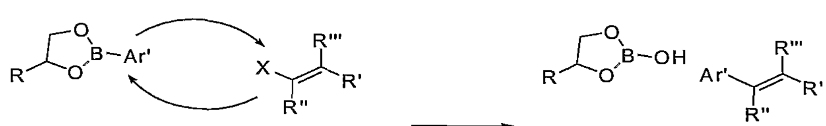
Q. Arylation

Biaryl formation by the reaction of Boronates with Aryls or Heteroaryls



R. Arylation

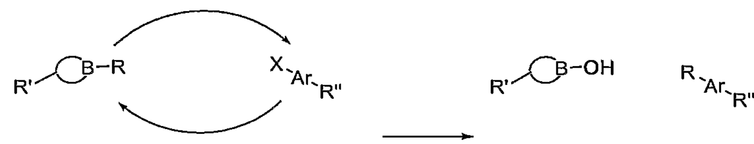
Vinylarene formation by the reaction of alkenes with Aryls or Heteroaryls



X = Halogen, OMs, OTf, OTos, etc

S. Alkylation

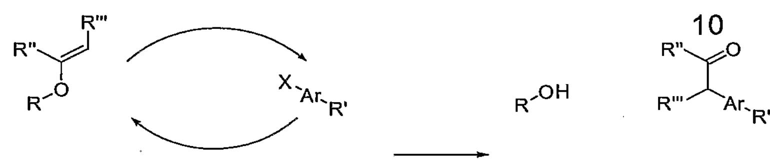
Alkylation of arenes/hetarens by the reaction with Alkyl boronates



X = Halogen, OMs, OTf, OTos, etc

T. Alkylation

Alkylation of arenas/hetarenes by reaction with enolethers

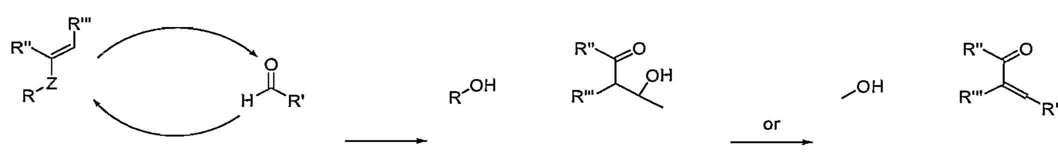


X = Halogen, OMs, OTf, OTos, etc

<u>Nucleophilic substitution using activation of nucleophiles</u>

U. Condensations

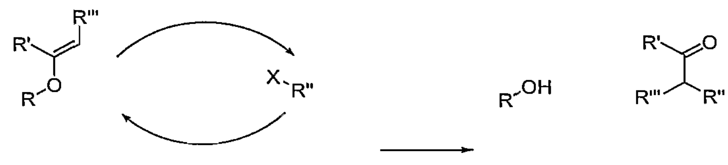
Alkylation of aldehydes with enolethers or enamines



Z = NR, O; X = Halogen, OMs, OTf, OTos, etc

V. Alkylation

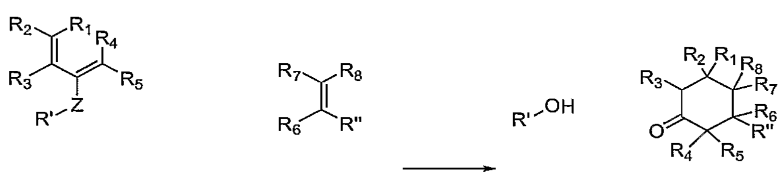
Alkylation of aliphatic halides or tosylates with enolethers or enamines



X = Halogen, OMs, OTf, OTos, etc

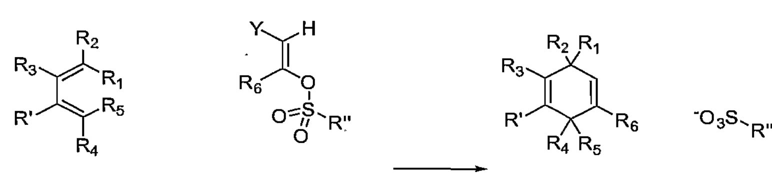
Cycloadditions

W. [2+4] Cycloadditions



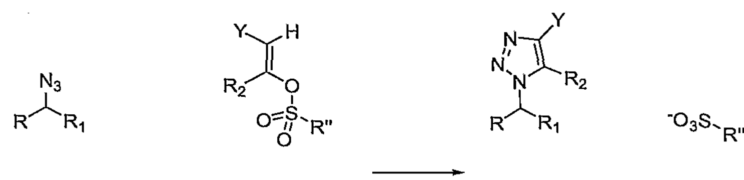
Z = O, NR

X. [2+4] Cycloadditions



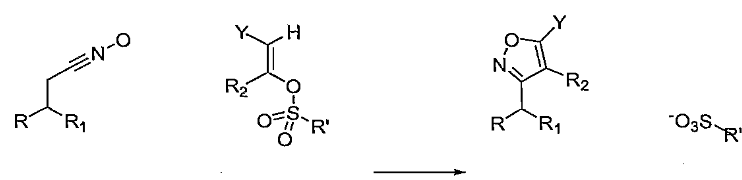
Y, CN, COOR, COR, NO_2, SO_2R, S(=O)R, SO_2NR_2, F

Y. [3+2] Cycloadditions



Y, CN, COOR, COR, NO_2, SO_2R, S(=O)R, SO_2NR_2, F

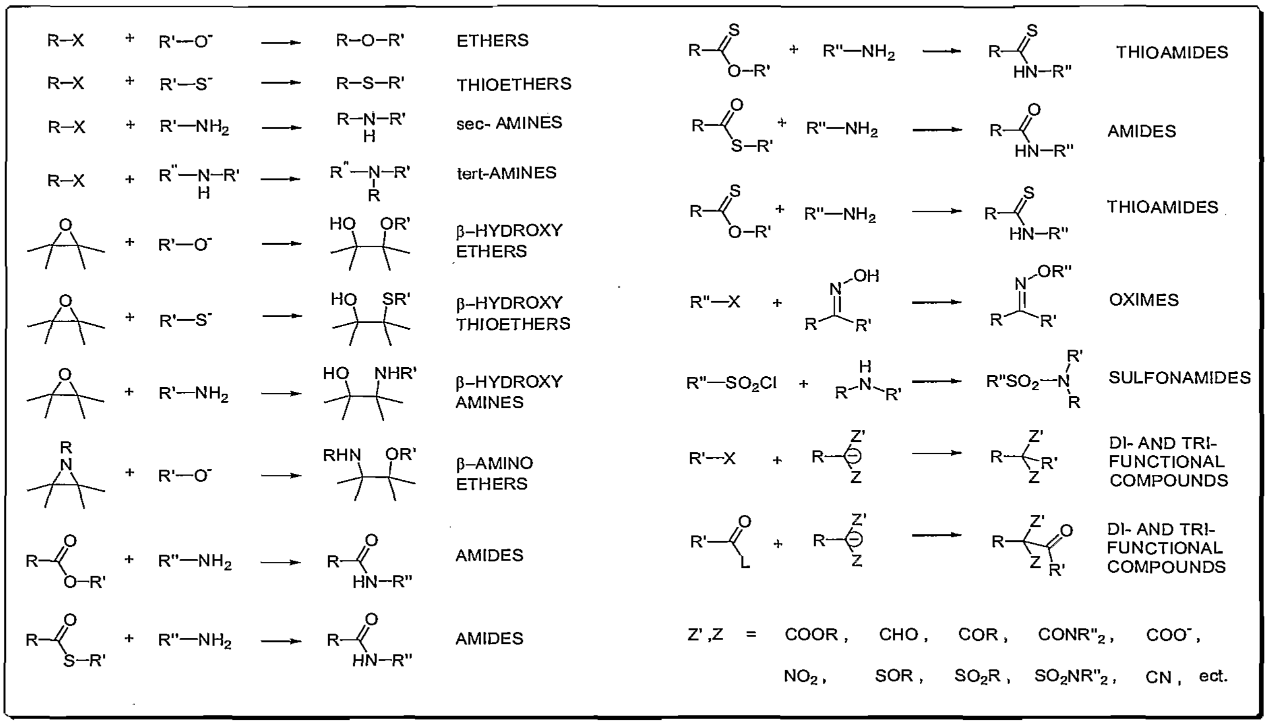
Z. [3+2] Cycloadditions



Y, CN, COOR, COR, NO_2, SO_2R, S(=O)R, SO_2NR_2, F

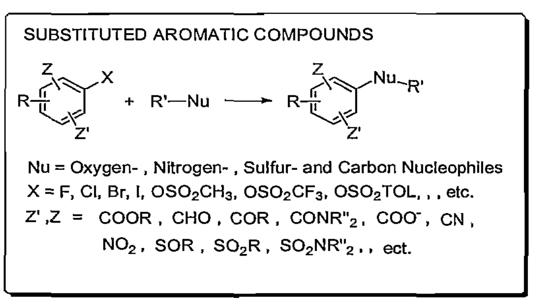
The synthesis of the molecule can involve one or more of the below illustrated reactions.

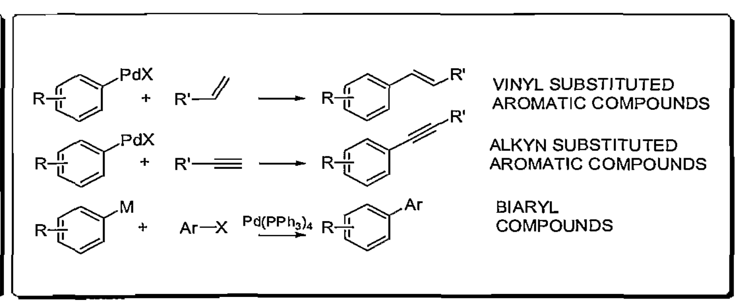
Examples of nucleophilic substitution reactions involved in one or more molecule synthesis steps.



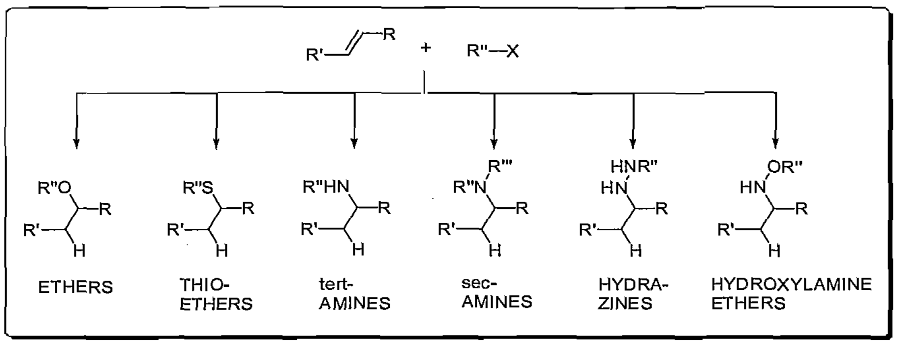
Aromatic nucleophilic substitutions

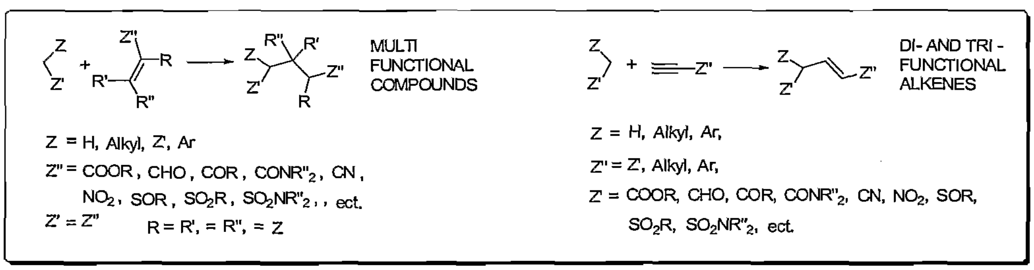
Transition metal catalysed reactions



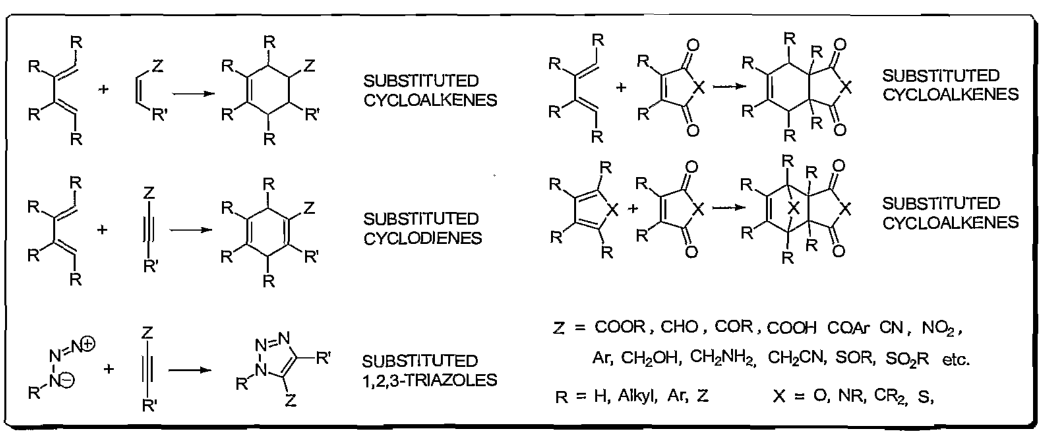


Addition to carbon-carbon multiple bonds

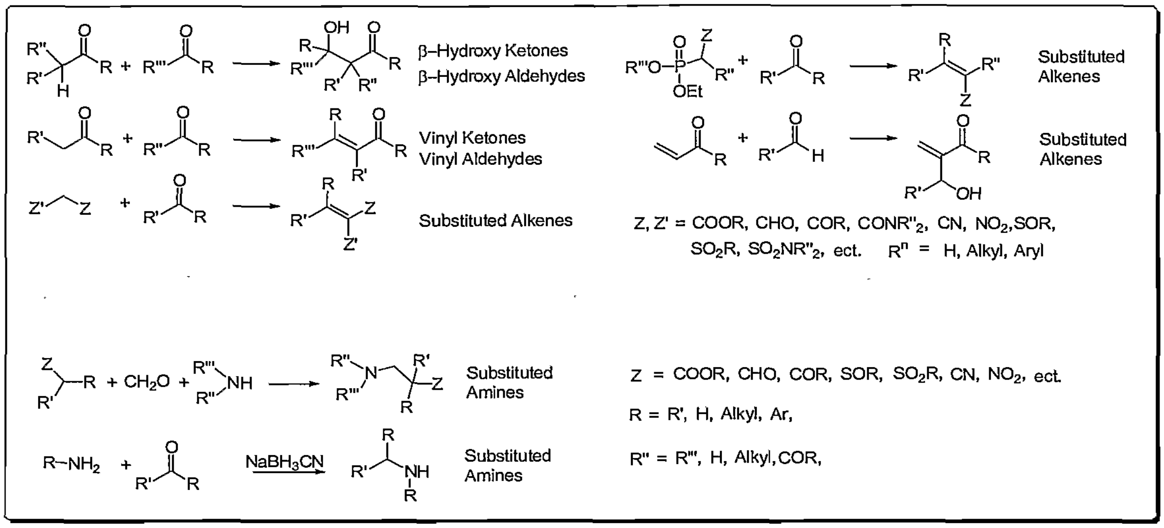




Cycloaddition to multiple bounds



Addition to carbon-hetero multiple bonds



In the above illustrated chemical reactions, R, R', R", R"', R"", R1, R2, R3, R4, R5, R6, R7, R8, respectively, are selected independently from the group consisting of: hydrido,

substituted and unsubstituted alkyl, substituted and unsubstituted haloalkyl, substituted and unsubstituted hydroxyalkyl, substituted and unsubstituted alkylsulfonyl,

substituted and unsubstituted alkenyl,

halo,

substituted and unsubstituted alkoxy, substituted and unsubstituted alkoxyalkyl, substituted and unsubstituted haloalkoxy, substituted and unsubstituted haloalkoxyalkyl,

substituted and unsubstituted aryl,

substituted and unsubstituted heterocyclic,

substituted and unsubstituted heteroaryl,

sulfonyl, substituted and unsubstituted alkylsulfonyl, substituted and unsubstituted arylsulfonyl, sulfamyl, sulfonamidyl, aminosulfonyl, substituted and unsubstituted N-alkylaminosulfonyl, substituted and unsubstituted N-arylaminosulfonyl, substituted and unsubstituted N,N-dialkylaminosulfonyl, substituted and unsubstituted N-alkyl-N-arylaminosulfonyl, substituted and unsubstituted N-alkylaminosulfonyl, substituted and unsubstituted N,N-dialkylaminosulfonyl, substituted and unsubstituted N-arylaminosulfonyl, substituted and unsubstituted N-alkyl-N-arylaminosulfonyl,

carboxy, substituted and unsubstituted carboxyalkyl,

carbonyl, substituted and unsubstituted alkylcarbonyl, substituted and unsubstituted alkylcarbonylalkyl,

substituted and unsubstituted alkoxycarbonyl, substituted and unsubstituted alkoxycarbonylalkyl,

aminocarbonyl, substituted and unsubstituted aminocarbonylalkyl, substituted and unsubstituted N-alkylaminocarbonyl, substituted and unsubstituted N-arylaminocarbonyl, substituted and unsubstituted N,N-dialkylaminocarbonyl, substituted and unsubstituted N-alkyl-N-arylaminocarbonyl, substituted and unsubstituted N-alkyl-N-hydroxyaminocarbonyl, substituted and unsubstituted N-alkyl-N-hydroxyaminocarbonylalkyl, substituted and unsubstituted N-alkylaminocarbonyl, substituted and unsubstituted N,N-dialkylaminocarbonyl, substituted and unsubstituted N-arylaminocarbonyl, substituted and unsubstituted N-alkyl-N-arylaminocarbonyl, substituted and unsubstituted aminocarbonylalkyl, substituted and unsubstituted N-cycloalkylaminocarbonyl,

substituted and unsubstituted aminoalkyl, substituted and unsubstituted alkylaminoalkyl,

amidino,

cyanoamidino,

substituted and unsubstituted heterocyclicalkyl,

substituted and unsubstituted aralkyl,

substituted and unsubstituted cycloalkyl,

substituted and unsubstituted cycloalkenyl,

substituted and unsubstituted alkylthio,

substituted and unsubstituted alkylsulfinyl,

substituted and unsubstituted N-alkylamino, substituted and unsubstituted N,N-dialkylamino,

substituted and unsubstituted arylamino, substituted and unsubstituted aralkylamino, substituted and unsubstituted N-alkyl-N-arylamino, substituted and unsubstituted N-aralkyl-N-alkylamino, substituted and unsubstituted N-arylaminoalkyl, substituted and unsubstituted N-aralkylaminoalkyl, substituted and unsubstituted N-alkyl-N-arylaminoalkyl, substituted and unsubstituted N-aralkyl-N-alkylaminoalkyl,

acyl, acylamino,

substituted and unsubstituted arylthio, substituted and unsubstituted aralkylthio,

substituted and unsubstituted aryloxy, substituted and unsubstituted aralkoxy,

substituted and unsubstituted haloaralkyl,

substituted and unsubstituted carboxyhaloalkyl,

substituted and unsubstituted alkoxycarbonylhaloalkyl, substituted and unsubstituted aminocarbonylhaloalkyl, substituted and unsubstituted alkylaminocarbonylhaloalkyl,

substituted and unsubstituted alkoxycarbonylcyanoalkenyl,

substituted and unsubstituted carboxyalkylaminocarbonyl,

substituted and unsubstituted aralkoxycarbonylalkylaminocarbonyl,

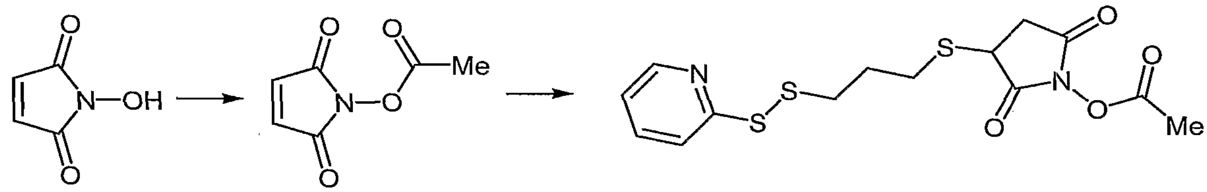
substituted and unsubstituted cycloalkylalkyl, and

substituted and unsubstituted aralkenyl.

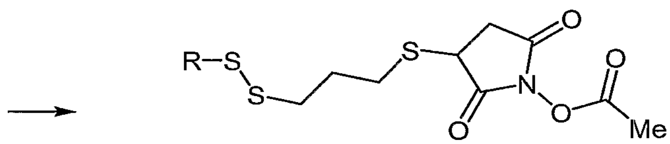
Further reaction schemes in accordance with the present invention are disclosed herein below.

A. Acylation reactions

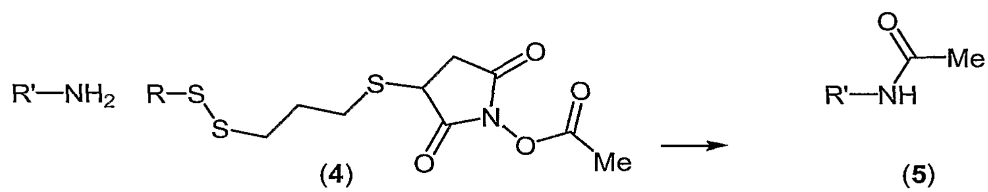
General route to the formation of acylating reactants and the use of these:



(1) (2) (3)



(4)



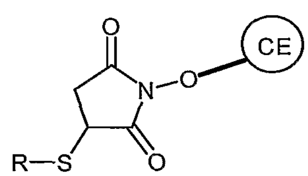
(4) (5)

N-hydroxymaleimide (**1**) may be acylated by the use of an acylchloride e.g. acetylchloride or alternatively acylated in e.g. THF by the use of dicyclohexylcarbodiimide or diisopropylcarbodiimide and acid e.g. acetic acid. The intermediate may be subjected to Michael addition by the use of excess 1,3-propanedithiol, followed by reaction with either 4,4'-dipyridyl disulfide or 2,2'-dipyridyl disulfide. This intermediate (**3**) may then be loaded onto an oligonucleotide carrying a thiol handle to generate the reactant (**4**). Obviously, the intermediate (**2**) can be attached to the oligonucleotide using another linkage than the disulfide linkage, such as an amide linkage and the N-hydroxymaleimide can be distanced from the oligonucleotide using a variety of spacers.

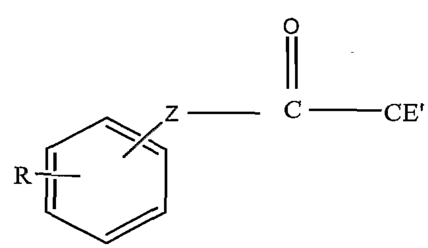
The reactant (**4**) may be reacted with an identifier oligonucleotide comprising a recipient amine group e.g. by following the procedure: The reactant (**4**) (1 nmol) is

mixed with an amino-oligonucleotide (1 nmol) in hepes-buffer (20 μL of a 100 mM hepes and 1 M NaCl solution, pH=7.5) and water (39 uL). The oligonucleotides are annealed together by heating to 50 °C and cooling (2 °C/ second) to 30 °C. The mixture is then left o/n at a fluctuating temperature (10 °C for 1 second then 35 °C for 1 second), to yield the product (**5**).

In more general terms, the reactants indicated below is capable of transferring a chemical entity (CE) to a recipient nucleophilic group, typically an amine group. The bold lower horizontal line illustrates the reactant and the vertical line illustrates a spacer. The 5-membered substituted N-hydroxysuccinimid (NHS) ring serves as an activator, i.e. a labile bond is formed between the oxygen atom connected to the NHS ring and the chemical entity. The labile bond may be cleaved by a nucleophilic group, e.g. positioned on a scaffold



Another reactant which may form an amide bond is



R may be absent or NO_2, CF_3, halogen, preferably Cl, Br, or I, and Z may be S or O. This type of reactant is disclosed in Danish patent application No. PA 2002 0951 and US provisional patent application filed 20 December 2002 with the title “A reactant capable of transferring a functional entity to a recipient reactive group”. The content of both patent application are incorporated herein in their entirety by reference.

A nucleophilic group can cleave the linkage between Z and the carbonyl group thereby transferring the chemical entity –(C=O)-CE' to said nucleophilic group.

CE and CE' are preferably selected from the group consisting of:

hydrido,

substituted and unsubstituted alkyl, substituted and unsubstituted haloalkyl, substituted and unsubstituted hydroxyalkyl, substituted and unsubstituted alkylsulfonyl,

substituted and unsubstituted alkenyl,

halo,

substituted and unsubstituted alkoxy, substituted and unsubstituted alkoxyalkyl, substituted and unsubstituted haloalkoxy, substituted and unsubstituted haloalkoxyalkyl,

substituted and unsubstituted aryl,

substituted and unsubstituted heterocyclic,

substituted and unsubstituted heteroaryl,

sulfonyl, substituted and unsubstituted alkylsulfonyl, substituted and unsubstituted arylsulfonyl, sulfamyl, sulfonamidyl, aminosulfonyl, substituted and unsubstituted N-alkylaminosulfonyl, substituted and unsubstituted N-arylaminosulfonyl, substituted and unsubstituted N,N-dialkylaminosulfonyl, substituted and unsubstituted N-alkyl-N-arylaminosulfonyl, substituted and unsubstituted N-alkylaminosulfonyl, substituted and unsubstituted N,N-dialkylaminosulfonyl, substituted and unsubstituted N-arylaminosulfonyl, substituted and unsubstituted N-alkyl-N-arylaminosulfonyl,

carboxy, substituted and unsubstituted carboxyalkyl,

carbonyl, substituted and unsubstituted alkylcarbonyl, substituted and unsubstituted alkylcarbonylalkyl,

substituted and unsubstituted alkoxycarbonyl, substituted and unsubstituted alkoxycarbonylalkyl,

aminocarbonyl, substituted and unsubstituted aminocarbonylalkyl, substituted and unsubstituted N-alkylaminocarbonyl, substituted and unsubstituted N-arylaminocarbonyl, substituted and unsubstituted N,N-dialkylaminocarbonyl, substituted and unsubstituted N-alkyl-N-arylaminocarbonyl, substituted and unsubstituted N-alkyl-N-hydroxyaminocarbonyl, substituted and unsubstituted N-alkyl-N-hydroxyaminocarbonylalkyl, substituted and unsubstituted N-alkylaminocarbonyl, substituted and unsubstituted N,N-dialkylaminocarbonyl, substituted and unsubstituted N-arylaminocarbonyl, substituted and unsubstituted N-alkyl-N-arylaminocarbonyl, substituted and unsubstituted aminocarbonylalkyl, substituted and unsubstituted N-cycloalkylaminocarbonyl,

substituted and unsubstituted aminoalkyl, substituted and unsubstituted alkylaminoalkyl,

amidino,

cyanoamidino,

substituted and unsubstituted heterocyclicalkyl,

substituted and unsubstituted aralkyl,

substituted and unsubstituted cycloalkyl,

substituted and unsubstituted cycloalkenyl,

substituted and unsubstituted alkylthio,

substituted and unsubstituted alkylsulfinyl,

substituted and unsubstituted N-alkylamino, substituted and unsubstituted N,N-dialkylamino,

substituted and unsubstituted arylamino, substituted and unsubstituted aralkylamino, substituted and unsubstituted N-alkyl-N-arylamino, substituted and unsubstituted N-aralkyl-N-alkylamino, substituted and unsubstituted N-arylaminoalkyl, substituted and unsubstituted N-aralkylaminoalkyl, substituted and unsubstituted N-alkyl-N-arylaminoalkyl, substituted and unsubstituted N-aralkyl-N-alkylaminoalkyl,

acyl, acylamino,

substituted and unsubstituted arylthio, substituted and unsubstituted aralkylthio,

substituted and unsubstituted aryloxy, substituted and unsubstituted aralkoxy,

substituted and unsubstituted haloaralkyl,

substituted and unsubstituted carboxyhaloalkyl,

substituted and unsubstituted alkoxycarbonylhaloalkyl, substituted and unsubstituted aminocarbonylhaloalkyl, substituted and unsubstituted alkylaminocarbonylhaloalkyl,

substituted and unsubstituted alkoxycarbonylcyanoalkenyl,

substituted and unsubstituted carboxyalkylaminocarbonyl,

substituted and unsubstituted aralkoxycarbonylalkylaminocarbonyl,

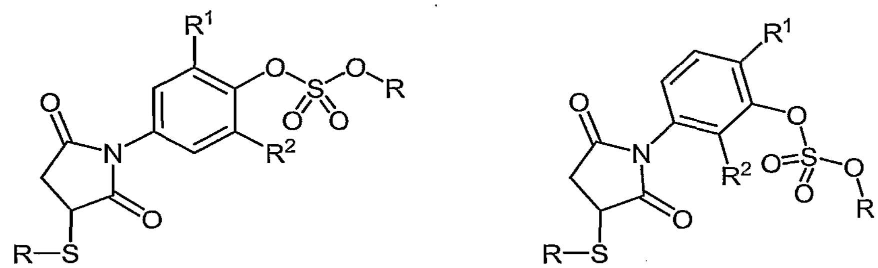
substituted and unsubstituted cycloalkylalkyl, and

substituted and unsubstituted aralkenyl.

B. Alkylation

General route to the formation of alkylating/vinylating reactants and use of these:

Alkylating reactants may have the following general structure:



R^1 = H, Me, Et, iPr, Cl, NO_2
R^2 = H, Me, Et, iPr, Cl, NO_2

R^1 and R^2 may be used to tune the reactivity of the sulphate to allow appropriate reactivity. Chloro and nitro substitution will increase reactivity. Alkyl groups will decrease reactivity. Ortho substituents to the sulphate will due to steric reasons direct incoming nucleophiles to attack the R-group selectively and avoid attack on sulphur.

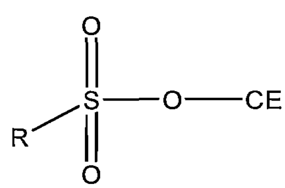
An example of the formation of an alkylating reactant and the transfer of a functional entity is depicted below:

3-Aminophenol (**6**) is treated with maleic anhydride, followed by treatment with an acid *e.g. H_2SO_4 or P_2O_5 and heated to yield the maleimide* (**7**). *The ring closure to* the maleimide may also be achieved when an acid stable *O*-protection group is used by treatment with Ac_2O, with or without heating, followed by *O*-deprotection. Alternatively reflux in Ac_2O, followed by *O*-deacetylation in hot water/dioxane to yield (**7**).
Further treatment of (**7**) with SO_2Cl_2, with or without triethylamine or potassium carbonate in dichloromethane or a higher boiling solvent will yield the intermediate (**8**), which may be isolated or directly further transformed into the aryl alkyl sulphate by the quench with the appropriate alcohol, in this case MeOH, whereby (**9**) will be formed.

The organic moiety (**9**) may be connected to an oligonucleotide, as follows: A thiol carrying oligonucleotide in buffer 50 mM MOPS or hepes or phosphate pH 7.5 is treated with a 1-100 mM solution and preferably 7.5 mM solution of the organic reactant (**9**) in DMSO or alternatively DMF, such that the DMSO/DMF concentration is 5-50%, and preferably 10%. The mixture is left for 1-16 h and preferably 2-4 h at 25 °C to give the alkylating agent in this case a methylating reactant (**10**).

The reaction of the alkylating reactant (**10**) with an amine bearing nascent bifunctional complex may be conducted as follows: The bifunctional complex (1 nmol) is mixed the reactant (**10**) (1 nmol) in hepes-buffer (20 µL of a 100 mM hepes and 1 M NaCl solution, pH=7.5) and water (39 uL). The oligonucleotides are annealed to each other by heating to 50 °C and cooled (2 °C/ second) to 30 °C. The mixture is then left o/n at a fluctuating temperature (10 °C for 1 second then 35 °C for 1 second), to yield the methylamine reaction product (**11**).

In more general terms, a reactant capable of transferring a chemical entity to a receiving reactive group forming a single bond is

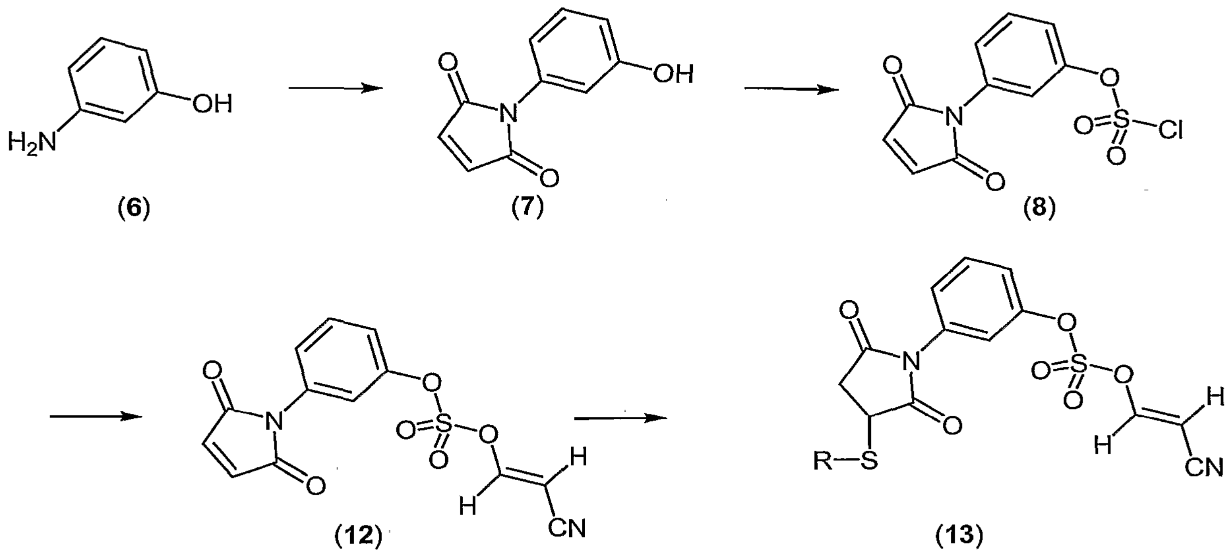


The receiving group may be a nucleophile, such as a group comprising a hetero atom, thereby forming a single bond between the chemical entity and the hetero atom, or the receiving group may be an electronegative carbon atom, thereby forming a C-C bond between the chemical entity and the scaffold.

CE is defined as herein above under section A (acylation reactions).

C. Vinylation reactions

A vinylating reactant may be prepared and used similarly as described above for an alkylating reactant. Although instead of reacting the chlorosulphonate (**8** above) with an alcohol, the intermediate chlorosulphate is isolated and treated with an enolate or *O*-trialkylsilylenolate with or without the presence of fluoride. E.g.

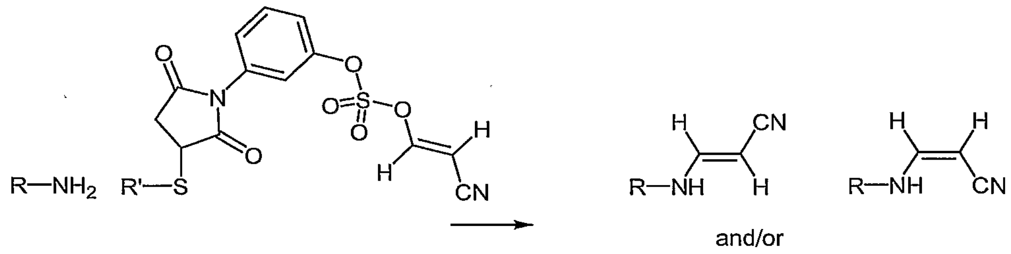


(6) (7) (8) (12) (13)

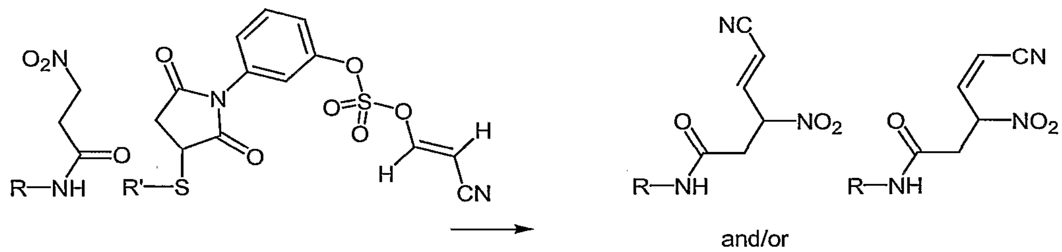
Formation of an exemplary vinylating reactant (**13**):

The thiol carrying oligonucleotide in buffer 50 mM MOPS or hepes or phosphate pH 7.5 is treated with a 1-100 mM solution and preferably 7.5 mM solution of the organic moiety (**12**) in DMSO or alternatively DMF, such that the DMSO/DMF concentration is 5-50%, and preferably 10%. The mixture is left for 1-16 h and preferably 2-4 h at 25 °C to give the vinylating reactant (**13**).

The sulfonylenolate (**13**) may be used to react with amine carrying scaffold to give an enamine (**14a** and/or **14b**) or e.g. react with a carbanion to yield (**15a** and/or **15b**). E.g.



(13) (14a) (14b)

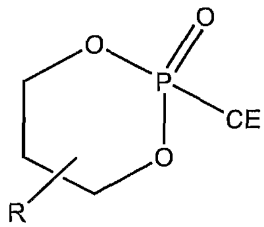


(13) (15a) (15b)

The reaction of the vinylating reactant (**13**) and an amine or nitroalkyl carrying identifier may be conducted as follows:

The amino-oligonucleotide (1 nmol) or nitroalkyl-oligonucleotide (1 nmol) identifier is mixed with the reactant (1 nmol) (**13**) in 0.1 M TAPS, phosphate or hepes-buffer and 300 mM NaCl solution, pH=7.5-8.5 and preferably pH=8.5. The oligonucleotides are annealed to the template by heating to 50 °C and cooled (2 °C/ second) to 30 °C. The mixture is then left o/n at a fluctuating temperature (10 °C for 1 second then 35 °C for 1 second), to yield reaction product (**14a/b** or **15a/b**). Alternative to the alkyl and vinyl sulphates described above may equally effective be sulphonates as e.g. (**31**) (however with R" instead as alkyl or vinyl), described below, prepared from (**28**, with the phenyl group substituted by an alkyl group) and (**29**), and be used as alkylating and vinylating agents.

Another reactant capable of forming a double bond by the transfer of a chemical entity to a recipient aldehyde group is shown below. A double bond between the carbon of the aldehyde and the chemical entity is formed by the reaction.



The above reactant is comprised by the Danish patent application No. DK PA 2002 01952 and the US provisional patent application filed 20 December 2002 with the title "A reactant capable of transferring a functional entity to a recipient reactive group forming a C=C double bond". The content of both patent applications are incorporated herein in their entirety by reference.

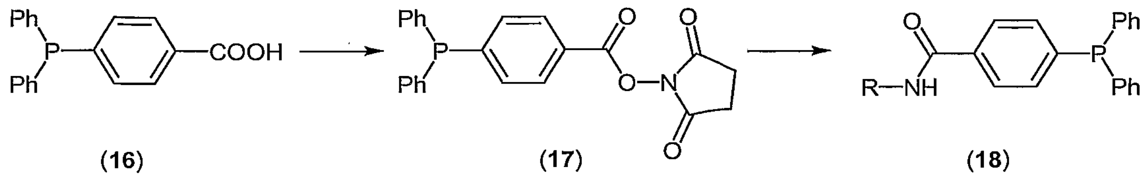
CE is defined as herein above under section A (acylation reactions).

D. Alkenylidation reactions

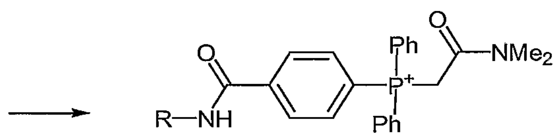
General route to the formation of Wittig and HWE reactants and use of these:

Commercially available compound (**16**) may be transformed into the NHS ester (**17**) by standard means, *i.e.* DCC or DIC couplings. An amine carrying oligonucleotide in buffer 50 mM MOPS or hepes or phosphate pH 7.5 is treated with a 1-100 mM solution and preferably 7.5 mM solution of the organic compound in DMSO or alternatively DMF, such that the DMSO/DMF concentration is 5-50%, and preferably 10%. The mixture is left for 1-16 h and preferably 2-4 h at 25 °C to give the phosphine bound precursor reactant (**18**). This precursor reactant is further transformed by addition of the appropriate alkylhalide, e.g. *N,N*-dimethyl-2-iodoacetamide as a 1-100 mM and preferably 7.5 mM solution in DMSO or DMF such that the DMSO/DMF concentration is 5-50%, and preferably 10%. The mixture is left for 1-16 h and preferably 2-4 h at 25 °C to give the reactant (**19**). As an alternative to this, the organic compound (**17**) may be *P*-alkylated with an alkylhalide and then be coupled onto an amine carrying oligonucleotide to yield (**19**).

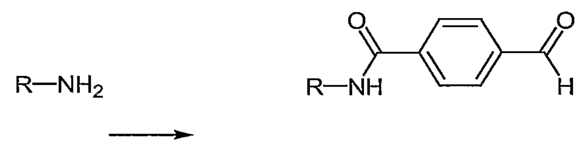
An aldehyde carrying identifier (**20**), may be formed by the reaction between the NHS ester of 4-formylbenzoic acid and an amine carrying oligonucleotide, using conditions similar to those described above. The identifier (**20**) reacts with (**19**) under slightly alkaline conditions to yield the alkene (**21**).



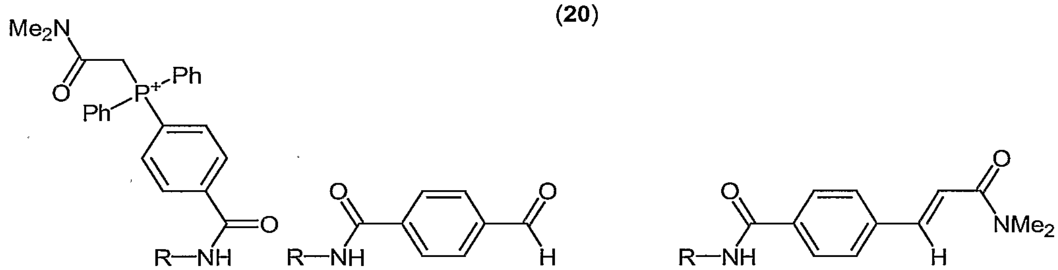
(16) (17) (18)



(19)



(20)



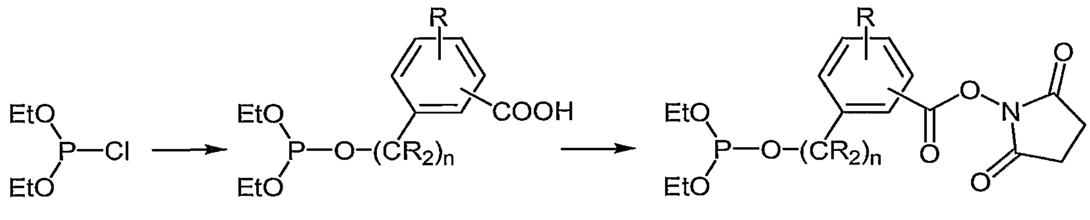
and *Z*-isomer

(19) (20) (21)

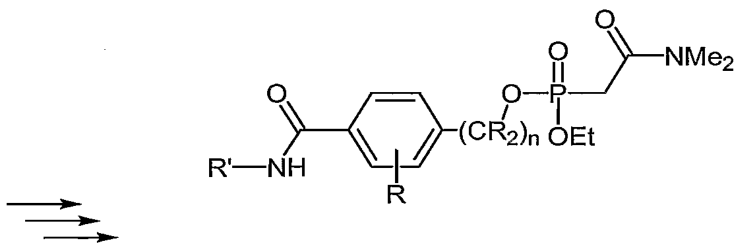
The reaction of monomer reactants (**19**) and identifier (**20**) may be conducted as follows: The identifier (**20**) (1 nmol) is mixed with reactant (**19**) (1 nmol) in 0.1 M TAPS, phosphate or hepes-buffer and 1 M NaCl solution, pH=7.5-8.5 and preferably pH=8.0. The reaction mixture is left at 35-65 °C preferably 58 °C over night to yield reaction product (**21**).

As an alternative to (**17**), phosphonates (**24**) may be used instead. They may be prepared by the reaction between diethylchlorophosphite (**22**) and the appropriate carboxy carrying alcohol. The carboxylic acid is then transformed into the NHS ester (**24**) and the process and alternatives described above may be applied. Although instead of a simple *P*-alkylation, the phosphite may undergo Arbuzov's reaction and

generate the phosphonate. Reactant (**25**) benefits from the fact that it is more reactive than its phosphonium counterpart (**19**).



(**22**) (**23**) n=0-2 (**24**)

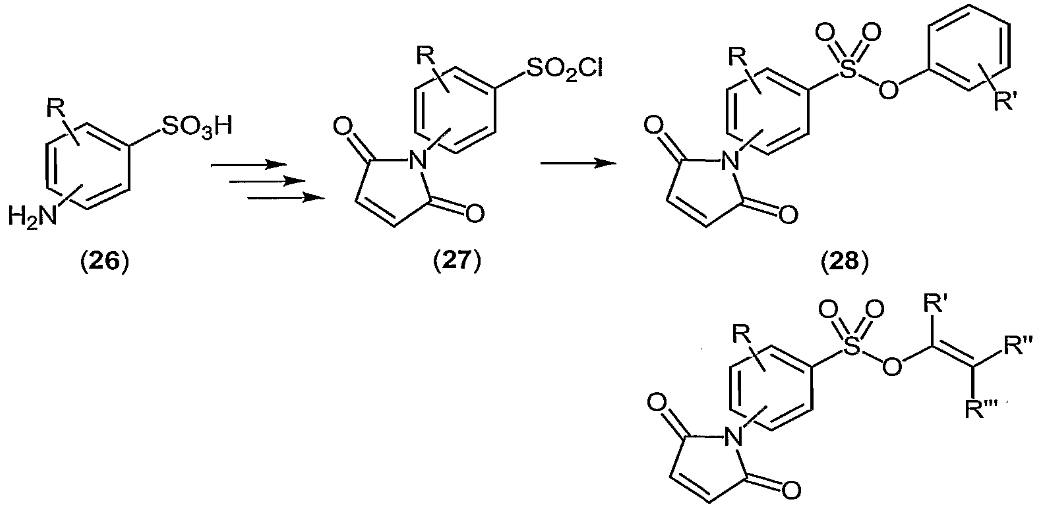


(**25**)

E. Transition metal catalyzed arylation, hetarylation and vinylation reactions

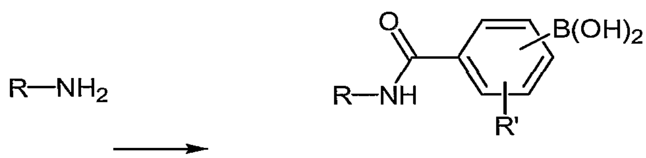
Electrophilic reactants (**31**) capable of transferring an aryl, hetaryl or vinyl functionality may be prepared from organic compounds (**28**) and (**29**) by the use of coupling procedures for maleimide derivatives to SH-carrying oligonucleotides described above. Alternatively to the maleimide the NHS-ester derivatives may be prepared from e.g. carboxybenzensulfonic acid derivatives, be used by coupling of these to an amine carrying oligonucleotide. The R-group of (**28**) and (**29**) is used to tune the reactivity of the sulphonate to yield the appropriate reactivity.

The transition metal catalyzed cross coupling may be conducted as follows: A premix of 1.4 mM Na_2PdCl_4 and 2.8 mM $P(p\text{-}SO_3C_6H_4)_3$ in water left for 15 min was added to a mixture of the identifier (**30**) and reactant (**31**) (both 1 nmol) in 0.5 M NaOAc buffer at pH=5 and 75 mM NaCl (final [Pd]=0.3 mM). The mixture is then left o/n at 35-65 °C preferably 58 °C, to yield reaction product (**32**).

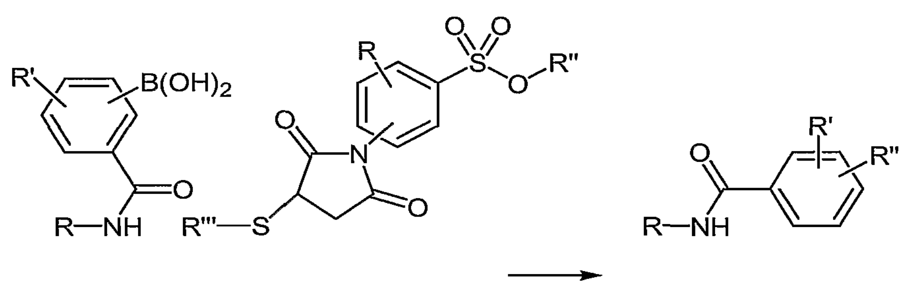


(26) (27) (28)

(29)



(30)



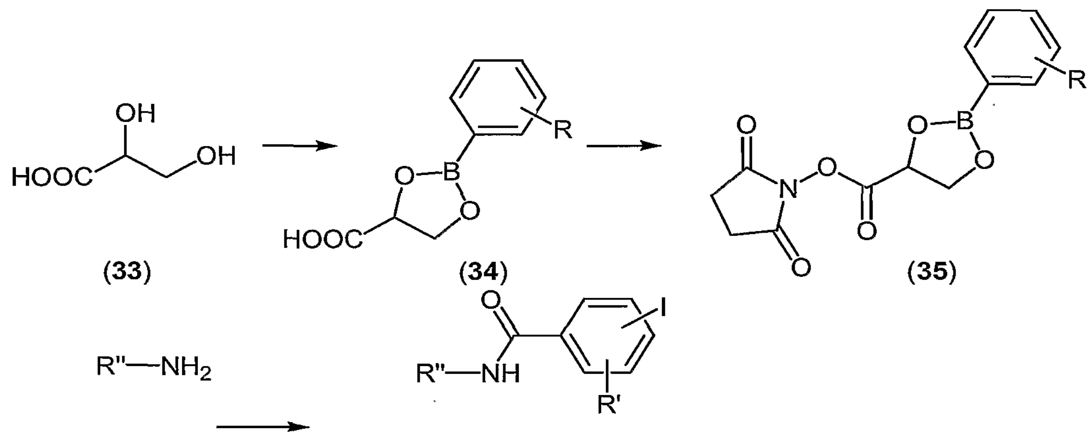
(30) (31) (32)

R'' = aryl, hetaryl or vinyl

Corresponding nucleophilic monomer reactants capable of transferring an aryl, hetaryl or vinyl functionality may be prepared from organic compounds of the type (**35**). This is available by estrification of a boronic acid by a diol e.g. (**33**), followed by transformation into the NHS-ester derivative. The NHS-ester derivative may then be coupled to an oligonucleotide, by use of coupling procedures for NHS-ester derivatives to amine carrying oligonucleotides described above, to generate reactant

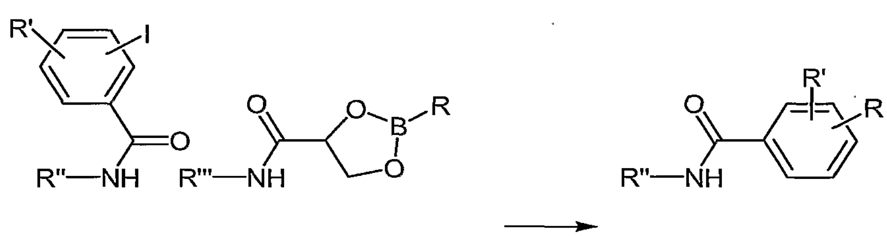
type (**37**). Alternatively, maleimide derivatives may be prepared as described above and loaded onto SH-carrying oligonucleotides.

The transition metal catalyzed cross coupling is conducted as follows:
A premix of 1.4 mM Na_2PdCl_4 and 2.8 mM $P(p\text{-}SO_3C_6H_4)_3$ in water left for 15 min was added to a mixture of the identifier (**36**) and the reactant (**37**) (both 1 nmol) in 0.5 M NaOAc buffer at pH=5 and 75 mM NaCl (final [Pd]=0.3 mM). The mixture is then left o/n at 35-65 °C preferably 58 °C, to yield template bound (**38**).



(**33**) (**34**) (**35**)

(**36**)



(**36**) (**37**) (**38**)

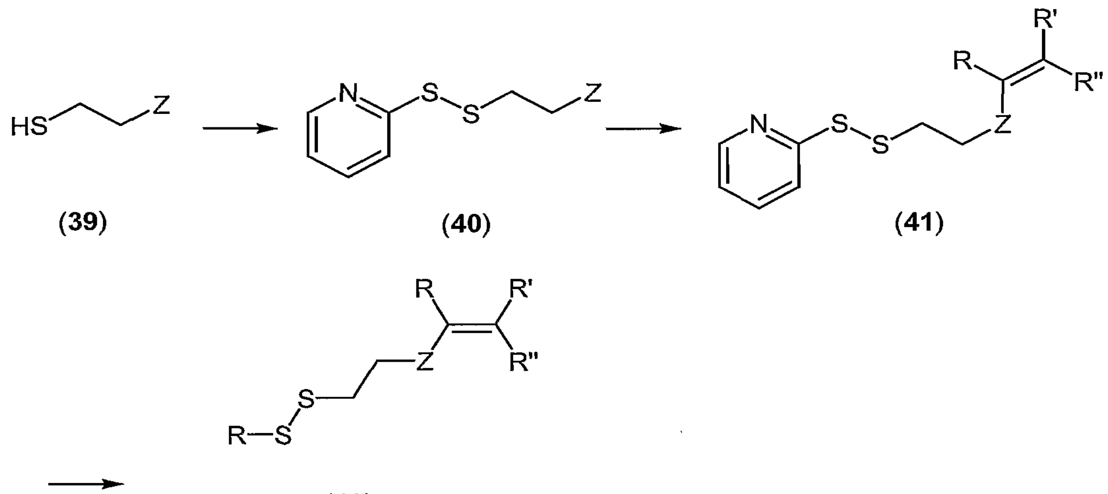
R = aryl, hetaryl or vinyl

F. Reactions of enamine and enolether monomer reactants

Reactants loaded with enamines and enolethers may be prepared as follows:
For Z=NHR (R=H, alkyl, aryl, hetaryl), a 2-mercaptoethylamine may be reacted with a dipyridyl disulfide to generate the activated disulfide (**40**), which may then be

condensed to a ketone or an aldehyde under dehydrating conditions to yield the enamine (**41**). For Z=OH, 2-mercaptoethanol is reacted with a dipyridyl disulfide, followed by *O*-tosylation (Z=OTs). The tosylate (**40**) may then be reacted directly with an enolate or in the presence of fluoride with a *O*-trialkylsilylenolate to generate the enolate (**41**).

The enamine or enolate (**41**) may then be coupled onto an SH-carrying oligonucleotide as described above to give the reactant (**42**).



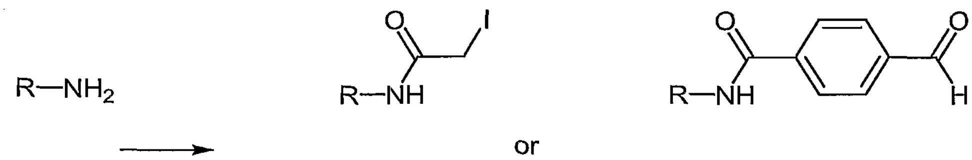
(39) (40) (41)

(42)

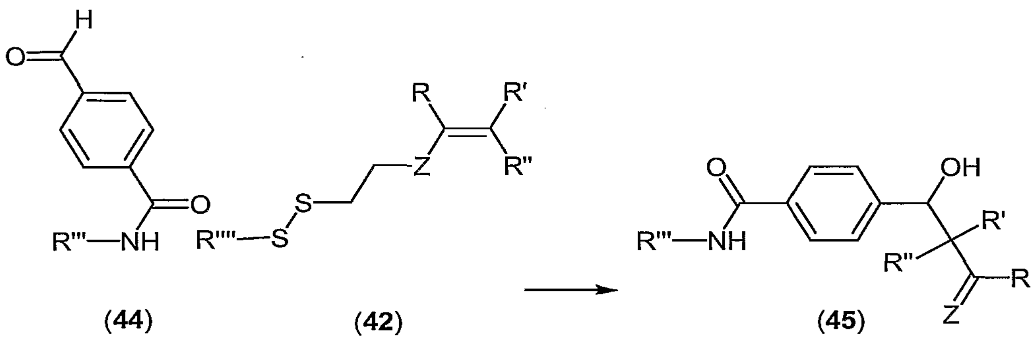
The reactant (**42**) may be reacted with a carbonyl carrying identifier oligonucleotide like (**44**) or alternatively an alkylhalide carrying oligonucleotide like (**43**) as follows: The reactant (**42**) (1 nmol) is mixed with the identifier (**43**) (1 nmol) in 50 mM MOPS, phosphate or hepes-buffer buffer and 250 mM NaCl solution, pH=7.5-8.5 and preferably pH=7.5. The reaction mixture is left at 35-65 °C preferably 58 °C over night or alternatively at a fluctuating temperature (10 °C for 1 second then 35 °C for 1 second) to yield reaction product (**46**), where Z=O or NR. For compounds where Z=NR slightly acidic conditions may be applied to yield product (**46**) with Z=O.

The reactant (**42**) (1 nmol) is mixed with the identifier (**44**) (1 nmol) in 0.1 M TAPS, phosphate or hepes-buffer buffer and 300 mM NaCl solution, pH=7.5-8.5 and preferably pH=8.0. The reaction mixture is left at 35-65 °C preferably 58 °C over night or alternatively at a fluctuating temperature (10 °C for 1 second then 35 °C for

1 second) to yield reaction product (**45**), where Z=O or NR. For compounds where Z=NR slightly acidic conditions may be applied to yield product (**45**) with Z=O.

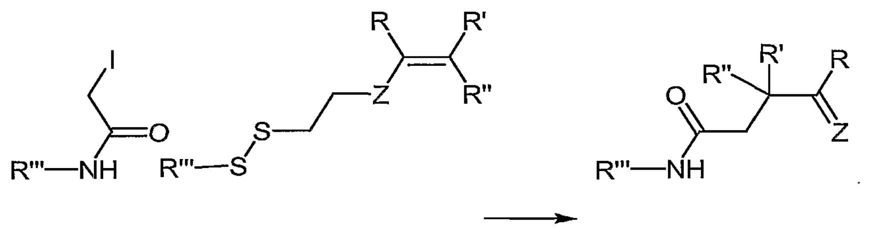


(**43**) (**44**)



(**44**) (**42**) (**45**)

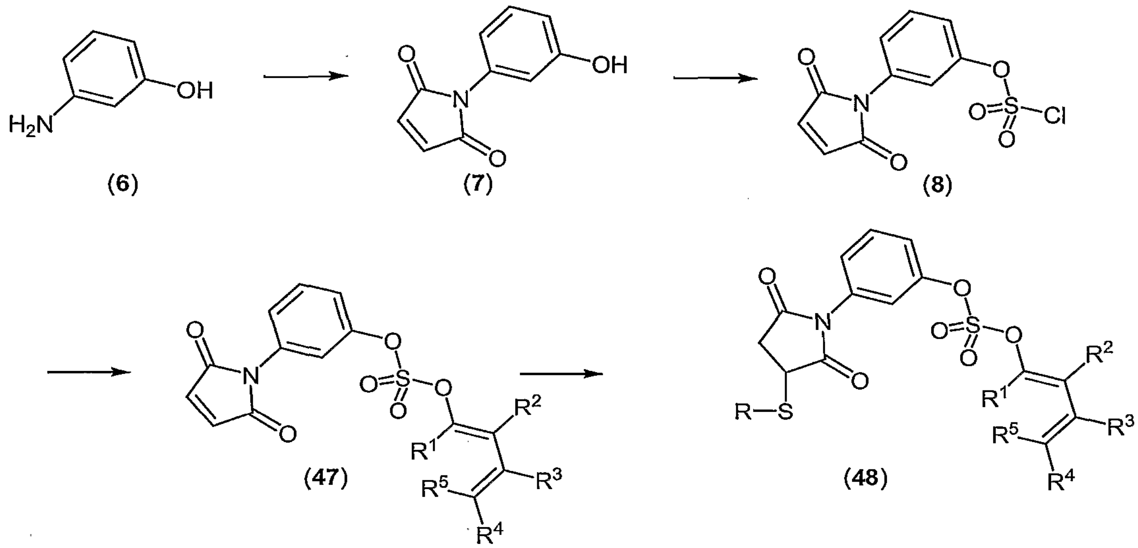
Z=O,NR



(**43**) (**42**) (**46**)

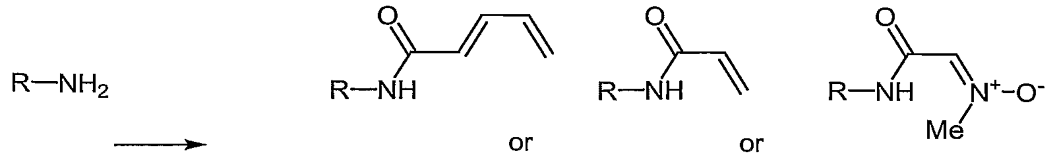
Z=O,NR

Enolethers type (**13**) may undergo cycloaddition with or without catalysis. Similarly, dienolethers may be prepared and used, e.g. by reaction of (**8**) with the enolate or trialkylsilylenolate (in the presence of fluoride) of an α,β-unsaturated ketone or aldehyde to generate (**47**), which may be loaded onto an SH-carrying oligonucleotide, to yield monomer reactant (**48**).

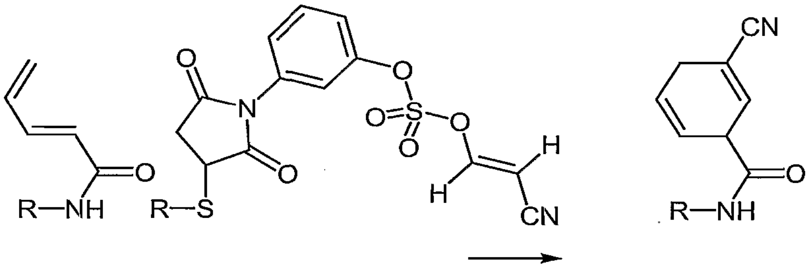


The diene (**49**), the ene (**50**) and the 1,3-dipole (**51**) may be formed by simple reaction between an amino carrying oligonucleotide and the NHS-ester of the corresponding organic compound. Reaction of (**13**) or alternatively (**31**, R"=vinyl) with dienes as e.g. (**49**) to yield (**52**) or e.g. 1,3-dipoles (**51**) to yield (**53**) and reaction of (**48**) or (**31**, R"=dienyl) with enes as e.g. (**50**) to yield (**54**) may be conducted as follows:

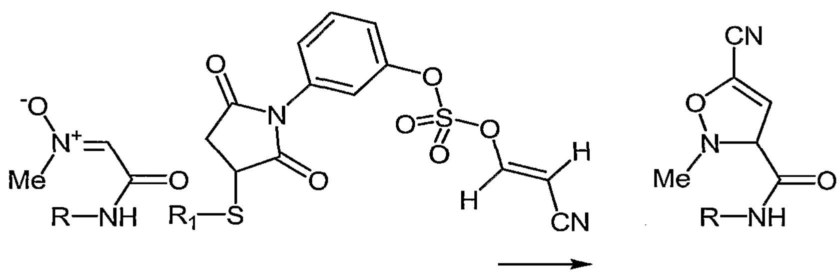
The reactant (**13**) or (**48**) (1 nmol) is mixed with the identifier (**49**) or (**50**) or (**51**) (1 nmol) in 50 mM MOPS, phosphate or hepes-buffer buffer and 2.8 M NaCl solution, pH=7.5-8.5 and preferably pH=7.5. The reaction mixture is left at 35-65 °C preferably 58 °C over night or alternatively at a fluctuating temperature (10 °C for 1 second then 35 °C for 1 second) to yield template bound (**52**), (**53**) or (**54**), respectively.



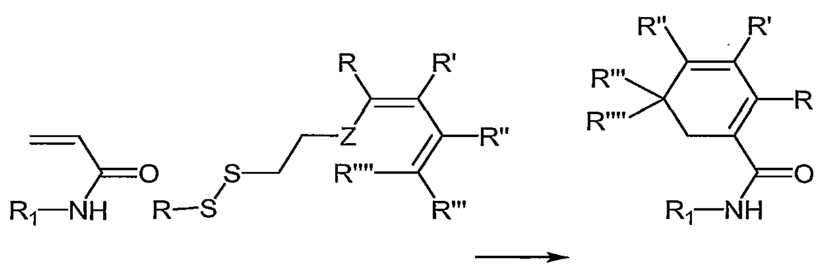
(49) (50) (51)



(49) (13) (52)



(51) (13) (53)

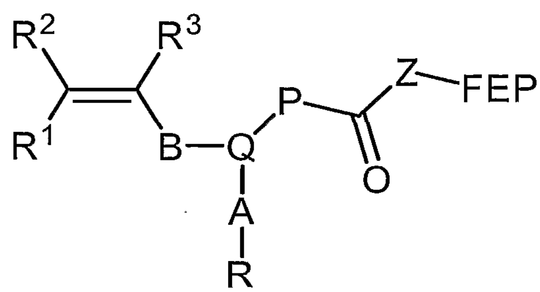


(50) (48) (54)

Cross-link cleavage reactants

It may be advantageous to split the transfer of a chemical entity to a recipient reactive group into two separate steps, namely a cross-linking step and a cleavage

step because each step can be optimized. A suitable reactant for this two step process is illustrated below:



Initially, a reactive group appearing on the functional entity precursor (abbreviated FEP) reacts with a recipient reactive group, e.g. a reactive group appearing on a scaffold, thereby forming a cross-link. Subsequently, a cleavage is performed, usually by adding an aqueous oxidising agent such as I_2, Br_2, Cl_2, H^+, or a Lewis acid. The cleavage results in a transfer of the group HZ-FEP- to the recipient moiety, such as a scaffold.

In the above formula

Z is O, S, NR^4

Q is N, CR^1

P is a valence bond, O, S, NR^4, or a group C_{5-7}arylene, C_{1-6}alkylene, C_{1-6}O-alkylene, C_{1-6}S-alkylene, NR^1-alkylene, C_{1-6}alkylene-O, C_{1-6}alkylene-S option said group being substituted with 0-3 R^4, 0-3 R^5 and 0-3 R^9 or C_1-C_3 alkylene-NR^4_2, C_1-C_3 alkylene-$NR^4C(O)R^8$, C_1-C_3 alkylene-$NR^4C(O)OR^8$, C_1-C_2 alkylene-O-NR^4_2, C_1-C_2 alkylene-O-$NR^4C(O)R^8$, C_1-C_2 alkylene-O-$NR^4C(O)OR^8$ substituted with 0-3 R^9,

B is a group comprising D-E-F, in which

D is a valence bond or a group C_{1-6}alkylene, C_{1-6}alkenylene, C_{1-6}alkynylene, C_{5-7}arylene, or C_{5-7}heteroarylene, said group optionally being substituted with 1 to 4 group R^{11},

E is, when present, a valence bond, O, S, NR^4, or a group C_{1-6}alkylene, C_{1-6}alkenylene, C_{1-6}alkynylene, C_{5-7}arylene, or C_{5-7}heteroarylene, said group optionally being substituted with 1 to 4 group R^{11},

F is, when present, a valence bond, O, S, or NR^4,

A is a spacing group distancing the chemical structure from the complementing element, which may be a nucleic acid,

R^1, R^2, and R^3 are independent of each other selected among the group consisting of H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_4-C_8 alkadienyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl, and heteroaryl, said group being substituted with 0-3 R^4, 0-3 R^5 and 0-3 R^9 or C_1-C_3 alkylene-NR^4_2, C_1-C_3 alkylene-$NR^4C(O)R^8$, C_1-C_3 alkylene-$NR^4C(O)OR^8$, C_1-C_2 alkylene-O-NR^4_2, C_1-C_2 alkylene-O-$NR^4C(O)R^8$, C_1-C_2 alkylene-O-$NR^4C(O)OR^8$ substituted with 0-3 R^9,

FEP is a group selected among the group consisting of H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_4-C_8 alkadienyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl, and heteroaryl, said group being substituted with 0-3 R^4, 0-3 R^5 and 0-3 R^9 or C_1-C_3 alkylene-NR^4_2, C_1-C_3 alkylene-$NR^4C(O)R^8$, C_1-C_3 alkylene-$NR^4C(O)OR^8$, C_1-C_2 alkylene-O-NR^4_2, C_1-C_2 alkylene-O-$NR^4C(O)R^8$, C_1-C_2 alkylene-O-$NR^4C(O)OR^8$ substituted with 0-3 R^9,

where R^4 is H or selected independently among the group consisting of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloheteroalkyl, aryl, heteroaryl, said group being substituted with 0-3 R^9 and

R^5 is selected independently from $-N_3$, -CNO, $-C(NOH)NH_2$, -NHOH, $-NHNHR^6$, $-C(O)R^6$, $-SnR^6_3$, $-B(OR^6)_2$, $-P(O)(OR^6)_2$ or the group consisting of C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_4-C_8 alkadienyl said group being substituted with 0-2 R^7,

where R^6 is selected independently from H, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, aryl or C_1-C_6 alkylene-aryl substituted with 0-5 halogen atoms selected from -F, -Cl, -Br, and –I; and R^7 is independently selected from $–NO_2$, $-COOR^6$, $-COR^6$, -CN, $-OSiR^6_3$, $-OR^6$ and $-NR^6_2$.

R^8 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, aryl or C_1-C_6 alkylene-aryl substituted with 0-3 substituents independently selected from –F, -Cl, $–NO_2$, $-R^3$, $-OR^3$, $-SiR^3_3$

R^9 is =O, -F, -Cl, -Br, -I, -CN, $-NO_2$, $-OR^6$, $-NR^6_2$, $-NR^6$-$C(O)R^8$, $-NR^6$-$C(O)OR^8$, $-SR^6$, $-S(O)R^6$, $-S(O)_2R^6$, $-COOR^6$, $-C(O)NR^6_2$ and $-S(O)_2NR^6_2$.

In a preferred embodiment Z is O or S, P is a valence bond, Q is CH, B is CH_2, and R^1, R^2, and R^3 is H. The bond between the carbonyl group and Z is cleavable with aqueous I_2.

Reactant reactions and molecules generated by such reactions

A reactant can participate in a reaction with the chemical reaction site and/or in a reaction with other reactants and contributes to the a chemical structure of the final molecule. The reaction between the chemical reaction site and the one or more

reactants, or between individual reactants, can take place under suitable conditions that favours the reaction.

Generally, a molecule is formed by reacting several chemical entities with each other and/or with a chemical reaction site, such as a scaffold moiety comprising a plurality of reactive groups or sites. In one embodiment of the invention, a nascent bifunctional complex is reacted with one or more reactants and with the respective tag(s) more than once preferably using a split-and-mix technique. The reactions can be repeated as often as necessary in order to obtain a molecule as one part of the bifunctional complex and an identifying oligonucleotide comprising the tags identifying the reactants which participated in the formation of the molecule.

The synthesis of a molecule according to the methods of the present invention can proceed via particular type(s) of coupling reaction(s), such as, but not limited to, one or more of the reactive group reactions cited herein above. In some embodiments, combinations of two or more reactive group reactions will occur, such as combinations of two or more of the reactive group reactions discussed above, or combinations of the reactions disclosed in Table 1. For example, reactants can be joined by a combination of amide bond formation (amino and carboxylic acid complementary groups) and reductive amination (amino and aldehyde or ketone complementary groups).

The reaction of the reactant(s) with each other and/or with the chemical reaction site on the one hand and the reaction of tag(s) with each other and/or with the priming site on the other hand may occur sequentially in any order or simultaneously. The choice of order can be influenced by e.g. type of enzyme, reaction conditions used, and the type of reactant(s). The chemical reaction site can comprise a single or multiple reactive groups capable of reacting with one or more reactants. In a certain aspect the chemical reaction site comprises a scaffold having one or more reactive groups attached.

A round or cycle of reaction can imply that a) a single reactant is reacted with the chemical reaction site, such as a scaffold, or with one or more reactant(s) having reacted with the chemical reaction site during a previous reaction round, and b) that the respective oligonucleotide tag identifying the reactant is reacted with another tag or with the priming site. However, a round or cycle of reaction can also imply that a)

multiple reactants are reacted with the chemical reaction site, such as a scaffold, or with one or more reactant(s) having reacted with the chemical reaction site during a previous reaction round, and b) that respective oligonucleotide tags identifying the reactants are reacted with each other and/or with another tag and/or with the priming site. At least one tag reaction resulting in the tag being attached to another tag or to the priming site involves one or more enzymes.

A reactant comprising one or more chemical entities and one or more reactive groups can have any chemical structure. At least one reactive group, or a precursor thereof, reacts with the chemical reaction site or one or more reactive group(s) of one or more other reactants. A "bridging molecule" can act to mediate a connection or form a bridge between two reactants or between a reactant and a chemical reaction site.

The invention can be performed by reacting a single reactant with the nascent bifunctional complex and add the corresponding tag. However, it may be preferred to build a molecule comprising the reaction product of two of more reactants. Thus, in a certain aspect of the invention a method is devised for obtaining a bifunctional complex composed of a molecule part and a single stranded identifier oligonucleotide, said molecule part being the reaction product of reactants and the chemical reaction site of the initial complex.

In one embodiment of the invention, parallel syntheses are performed so that a tag is enzymatical linked to a nascent bifunctional complex in parallel with a reaction between a chemical reaction site and a reactant. In each round the addition of the tag is followed or preceded by a reaction between reactant and the chemical reaction site. In each subsequent round of parallel syntheses the reaction product of the previous reactions serves as the chemical reaction site and the last-incorporated tag provides for a priming site which allows for the enzymatical addition a tag. In other aspects of the invention, two or more tags are provided prior to or subsequent to reaction with the respective reactants.

The single stranded identifier oligonucleotide comprising covalently ligated tags can be transformed to a double stranded form by an extension process in which a primer is annealed to the 3' end of the single stranded identifier oligonucleotide and

extended using a suitable polymerase. The double strandness can be an advantage during subsequent selection processes.

Reactants comprising chemical entities and reactive groups can be synthesised e.g. as disclosed by Dolle *et al.* (Dolle, R. E. Mol. Div.; 3 (1998) 199-233; Dolle, R. E. Mol. Div.; 4 (1998) 233-256; Dolle, R. E.; Nelson, K. H., Jr. *J. Comb. Chem.;* **1** (1999) 235-282; Dolle, R. E. *J. Comb. Chem.;* **2** (2000) 383-433; Dolle, R. E. *J. Comb. Chem.;* **3** (2001) 477-517; Dolle, R. E. *J. Comb. Chem.;* **4** (2002) 369-418; Dolle, R. E. *J. Comb. Chem.;* **5** (2003) 693-753; Dolle, R. E. *J. Comb. Chem.;* **6** (2004) 623-679; Dolle, R. E. *J. Comb. Chem.;* **7** (2005) 739-798; Dolle, R. E.; Le Bourdonnec, B.; Morales, G. A.; Moriarty, K. J.; Salvino, J. M., *J. Comb. Chem.;* **8** (2006) 597-635 and references cited therein. (incorporated by reference herein in their entirety).

Reactants may furthermore be formed by use of solid phase synthesis or by in solution synthesis. Reactants may also be commercially available. Reactants may be produced by conventional organic synthesis, parallel synthesis or combinatorial chemistry methods.

Protection groups

Reactive groups may optionally be protected using protection group chemistries as e.g. described by Green T.W. and Wuts P.G.M in Protection Groups in Organic Synthesis, Wiley, 1999, ISBN: 0-471-16019-9 which is hereby incorporated by reference.

In one embodiment amines may optionally be protected as carbamates, such as for example methyl carbamate, ethyl carbamate, t-butyl carbamate (Boc), 9-fluorenylmethyl carbamate (Fmoc), 2,2,2-trichlorethyl carbamate, 2-trimethylsilylethyl carbamate, vinyl carbamate, allyl carbamate, benzyl carbamate, p-methoxybenzyl carbamate, p-nitrobenzyl carbamate, m-nitrophenyl carbamate, 3,5-dimethoxybenzyl carbamate, alpha-methylnitropiperonyl carbamate, o-nitrophenyl carbamate, 3,4-dimethoxy-6-nitro carbamate, phenyl(o-nitrophenyl)methyl carbamate, 2-(2-nitrophenyl)ethyl carbamate, 6-nitroveratryl carbamate, 4-methoxyphenacyl carbamate, methylsulfonylethyl carbamate (MSc), which may optionally be deprotected as appropriate according to literature procedures as

described by Green T.W. and Wuts P.G.M in *Protection Groups in Organic Synthesis*, Wiley, 1999.

In another embodiment amines may optionally be protected as amides, such as for example trifluoroacetamide, trichloroacetamide, 4-pentenoic acid amide, o-(benzoyloxymethyl)benzamide, 2-(acetoxymethyl)benzamide, N-phthalimide, N-tetrachlorophthalimide, a nosyl (Ns) protection group, such as for example an o-nitrophenylsulfonamide (o-Ns), for example an p-nitrophenylsulfonylsulfonamide (p-Ns), which may optionally be deprotected as appropriate according to literature procedures as described by Green T.W. and Wuts P.G.M in *Protection Groups in Organic Synthesis*, Wiley, 1999.

In a further embodiment amines may optionally be protected as triphenylmethyl amine (trityl, Trt), di(p-methoxyphenyl)phenylmethyl (DMT) amine, which may optionally be deprotected as appropriate according to literature procedures as described by Green T.W. and Wuts P.G.M in *Protection Groups in Organic Synthesis*, Wiley, 1999.

In one embodiment carboxylic acids may optionally be protected such as for example methyl ester, ethyl ester, t-butyl ester, benzyl ester, p-methoxy benzyl ester, 9-fluorenylmethyl ester, methoxy methyl ester, benzyloxy methyl ester, cyanomethyl ester, phenacyl ester, p-methoxy phenacyl ester, 2,2,2-trichloroethyl ester, vinyl ester, allyl ester, triethylsilyl ester, t-butyldimethylsilyl ester, phenyldimethylsilyl ester, triphenylmethyl ester, di(p-methoxyphenyl)phenylmethyl ester, methyl sulfonylethyl ester, which may optionally be deprotected as appropriate according to literature procedures as described by Green T.W. and Wuts P.G.M in *Protection Groups in Organic Synthesis,* Wiley, 1999.

In one embodiment hydroxyl groups may optionally be protected such as for example methyl ether, methoxymethyl ether, benzyloxymethyl ether, p-methoxybenzyloxymethyl ether, o-nitrobenzyloxymethyl ether, tetrahydropyranyl ether, tetrahydrofuranyl ether, ethoxyethyl ether, 2,2,2-trichloroethyl ether, allyl ether, vinyl ether, benzyl ether, p-methoxybenzyl ether, o-nitrobenzyl ether, triphenylmethyl ether, di(p-methoxyphenyl)phenylmethyl ether, which may optionally be deprotected as appropriate according to literature procedures as described by

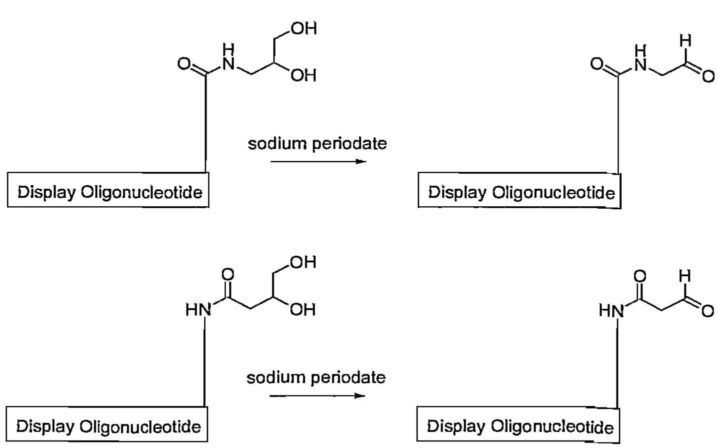
Green T.W. and Wuts P.G.M in *Protection Groups in Organic Synthesis*, Wiley, 1999.

In another embodiment hydroxyl groups may optionally be protected such as for example formic acid ester, acetic acid ester, trichloroacetic acid ester, trifluoroacetic acid ester, which may optionally be deprotected as appropriate according to literature procedures as described by Green T.W. and Wuts P.G.M in *Protection Groups in Organic Synthesis*, Wiley, 1999.

In a further embodiment hydroxyl groups may optionally be protected such as for example methyl carbonates, methoxymethyl carbonates, 9-fluorenylmethyl carbonates, ethyl carbonates, 2,2,2-trichloroethyl carbonates, allyl carbonates, vinyl carbonates, t-butyl carbonates, benzyl carbonates, p-methoxybenzyl carbonates, tosylate, which may optionally be deprotected as appropriate according to literature procedures as described by Green T.W. and Wuts P.G.M in *Protection Groups in Organic Synthesis*, Wiley, 1999.

In one embodiment carbonyl groups may optionally be protected such as for example dimethyl acetal and ketal, dibenzyl acetal and ketal, 1,3-dioxanes, 1,3-dioxolanes, 1,3-dithiane, 1,3-dithiolane, S,S'-dimethyl thioacetal and ketal, which may optionally be deprotected as appropriate according to literature procedures as described by Green T.W. and Wuts P.G.M in *Protection Groups in Organic Synthesis*, Wiley, 1999.

In another embodiment aldehydes may optionally be masked as 1,2-diols, which may optionally bedemasked by use of periodate. For example:



1. Dry down 1-20 nmol diol functionalised oligo
2. Add 25 µl $NaIO_4$ (50 mM in Sodium Acetate Buffer pH 4)
3. Shake at 25 °C for 30 min.
4. Add 25 µl 700mM Phosphate buffer pH 6.7
5. Purify by P6 spin column
6. Dry down the aldehyde functionalized oligo (temperature max. 45 °C)

The following procedures may be applied for deprotection of protection groups. Other methods may also be applied as described in the literature and by Green T.W. and Wuts P.G.M in *Protection Groups in Organic Synthesis*, Wiley, 1999:

Procedure for tBu ester and N-Boc deprotection

1. Dry down functionalised oligo in an PCR tube
2. Add 20 µL 37.5 mM NaOAc and 5 µL 1 M $MgCl_2$
3. Incubate at 70 °C ON (Lid 100 °C) in PCR-machine
4. Add 45 µL H_2O
5. Purify by P6 spin column

Procedure Fmoc deprotection in water

1. Dry down oligo
2. Add 6% piperidine/H_2O 10 µL
3. Shake 30 min at 25 °C.
4. Add 40 µL H_2O
5. Purify by P6 spin column

Procedure Msc deprotection in water

1. Dry down oligo
2. Dissolve in 25 µL Sodium Borate Buffer (0.1 M, pH=10)
3. Shake 3h at 40 °C
4. Add 25 µL Water
5. Purify by P6 spin column

Deprotection of tBu, Me and Et esters

1. Dry down oligo in an PCR tube
2. Add 20 µL 100 mM LiOH, seal tube
3. Incubate at 80 °C in PCR machine for 30 minutes
4. Add 40 µL 100 mM NaOAc buffer pH 5
5. Purify by P6 spin column

Procedure for Fmoc deprotection on DEAE sepharose

1) 100 µL DEAE suspension is pipetted into a filtertube and drained by vacuum.
2) Add water (200 µL) and drain.
3) Bind solution (H_2O (200 µL)) is added. Shake 10 min 600 rpm, then drain.
4) Bind solution (H_2O (100 µL) is added. No drain!
5) Oligo dissolved in H_2O (max. 50 µL) is added. Shake 10 min 600 rpm, then drain.
6) H_2O is added (200 µL). Drain.
7) DMF is added (200 µL). Drain.
8) Repeat step 11 twice.
9) 10% piperidine/DMF (250 µL) is added. Shake 5 min 600 rpm. Spin 1000 g 1 min.
10) Repeat step 13.
11) DMF is added (200 µL). Drain.
12) Repeat step 15 twice
13) H_2O is added (200 µL). Drain.
14) Repeat step 17
15) Release solution is added (35 µL, 2M TEAB). Shake 10 min 600 rpm. Spin at 1000 g for 1 min, collect the solvent in an eppendorf tube.
16) Repeat step 19.
17) Combine the solvents from step 19 and 20, then spin column filtrate the sample.

Procedure for Ns deprotection on DEAE sepharose

1) 100 µL DEAE suspension is pipetted into a filtertube and drained by vacuum.
2) Add water (200 µL) and drain.
3) Bind solution (H_2O (200 µL)) is added. Shake 10 min 600 rpm, then drain.
4) Bind solution (H_2O (100 µL) is added. No drain!
5) Oligo dissolved in H_2O (max. 50 µL) is added. Shake 10 min 600 rpm, then drain.
6) H_2O is added (200 µL). Drain.
7) DMF (dry) is added (200 µL). Drain.
8) Repeat step 7 twice.
9) 0.5M mercaptoanisol and 0.25M DIPEA in DMF (dry) (200 µL; freshly prepared) is added. Shake 24h at 25 °C, 600 rpm. No drain!
10) 0.3 M AcOH in DMF is added (200 µL). Shake 5 min 600 rpm, then drain.
11) DMF is added (200 µL). Drain.
12) Repeat step 11 twice
13) H_2O is added (200 µL). Drain.
14) Repeat step 13
15) Release solution is added (35 µL, 2M TEAB). Shake 10 min 600 rpm. Spin at 1000 g for 1 min, collect the solvent in an eppendorf tube.
16) Repeat step 15.
17) Combine the solvents from step 14 and 15, then spin column filtrate the sample.

<u>Procedure for Ns deprotection on DEAE sepharose (parallel format)</u>

1) 20µL DEAE suspension is pipetted into each well and drained by vacuum. (The capacity of the DEAE suspension is 0.5nmol/µL oligo use min 20 µL for >10 nmol oligo)
2) Add water (100 µL per well) and drain.
3) Bind solution (H_2O (100 µL per well)) is added. Shake 10 min 600 rpm, then drain.
4) Oligo dissolved in H_2O (max. 100 µL per well) is added. Shake 10 min 600 rpm, then drain.
5) H_2O is added (100 µL per well). Drain.
6) DMF (dry) is added (100 µL per well). Drain.
7) Repeat step 6 twice.
8) 0.5M mercaptoanisol and 0.25M DIPEA in DMF (dry) (100 µL per well; freshly prepared) is added. Shake 24h at 25 °C, 600 rpm. No drain!

9) 0.3 M AcOH in DMF is added (100 µL per well). Shake 5 min 600 rpm, then drain.
10) DMF is added (100 µL per well). Drain.
11) Repeat step 10 twice
12) H_2O is added (100 µL per well). Drain.
13) Repeat step 12
14) Release solution is added (50 µL per well, 2M TEAB). Shake 10 min 600 rpm. Spin at 1000 g for 1 min, collect the solvent in a 96 well plate.
15) Repeat step 14.
16) Combine the solvents from step 14 and 15, then evaporate samples to ~50 µL per well and spin column filtrate the samples.

A reactant can include one or more functional groups in addition to the reactive group or groups employed to generate the molecule being synthesised by the methods of the present invention. One or more of the functional groups can be protected to prevent undesired reactions of these functional groups. Suitable protecting groups are known in the art for a variety of functional groups (see e.g. Greene and Wuts, Protective Groups in Organic Synthesis, second edition, New York: John Wiley and Sons (1991), incorporated herein by reference). Useful protecting groups include t-butyl esters and ethers, acetals, trityl ethers and amines, acetyl esters, trimethylsilyl ethers,trichloroethyl ethers and esters and carbamates.

The reactive groups of the reactants and/or the chemical reaction site can also be in a pro-form that has to be activated before a reaction with (another) reactant can take place. As an example, the reactive groups can be protected, c.f. above, with a suitable group, which needs to be removed before a reaction with the reactant can proceed. Accordingly, a reactant can comprise one or more reactive group(s) or precursors of such groups, wherein the precursors can be activated or processed to generate the reactive group. Also, the reactant itself can be a precursor for the structural entity which is going to be incorporated into the display molecule.

Examples of further protection groups include "N-protected amino" and refers to protecting groups protecting an amino group against undesirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in Greene, "Protective Groups In Organic Synthesis," (John Wiley & Sons, New York (1981)). Preferred N-protecting groups are formyl, acetyl, benzoyl, pivaloyl, t-butyl-acetyl,

phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc), and benzyloxycarbonyl (Cbz).

Also, the term "O-protected carboxy" refers to a carboxylic acid protecting ester or amide group typically employed to block or protect the carboxylic acid functionality while the reactions involving other functional sites of the compound are performed. Carboxy protecting groups are disclosed in Greene, "Protective Groups in Organic Synthesis" (1981). Additionally, a carboxy protecting group can be used as a prodrug whereby the carboxy protecting group can be readily cleaved in vivo, for example by enzymatic hydrolysis, to release the biologically active parent. Such carboxy protecting groups are well known to those skilled in the art, having been extensively used in the protection of carboxyl groups in the penicillin and cephalosporin fields as described in U.S. Pat. Nos. 3,840,556 and 3,719,667.

In some embodiments, the reaction between reactans or between a reactant and the chemical reaction site can involve a further reactant, such as a “bridging-molecule”, mediating a connection between the reactant and the chemical reaction site.

Scaffolds and small molecules

In some embodiments, the chemical reaction site comprises one or more scaffolds each having one or more reactive groups attached thereto. The one or more reactive groups can e.g. be any of the groups cited herein above under the heading “Chemical reaction site and reactive groups”.

Examples of scaffold structures are e.g. benzodiazepines, steroids, hydantiones, piperasines, diketopiperasines, morpholines, tropanes, cumarines, qinolines, indoles, furans, pyrroles, oxazoles, amino acid precursors, and thiazoles. Further examples are provided herein below.

When the synthesis methods employ scaffolds, a reactant comprising only one reactive group can be used in the end position of the scaffolded molecule being synthesised, whereas reactants comprising two or more reactive groups are suitably incorporated into the body part and/or a branching portion of a scaffolded molecule optionally capable of being reacted with further reactants. Two or more reactive groups can be present on a scaffold having a core structure on which the molecule is being synthesised. This create the basis for synthesising multiple variants of

compounds of the same class or compounds sharing certain physical or functional traits. The variants can be formed e.g. through reaction of reactive groups of the scaffold with reactive groups of one or more reactants, optionally mediated by fill-in groups ("bridging molecules") and/or catalysts.

The small molecules of the compound libraries of the present invention can be linear, branched or cyclical, or comprise structural elements selected from a combination of the aforementioned structures. When comprising a ring system, the small molecules can comprise a single ring or a fused ring system. One or more heteroatoms can be present in either the single ring system or the fused ring system.

"Single ring" refers to a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl ring having about three to about eight, or about four to about six ring atoms. A single ring is not fused by being directly bonded at more than one ring atom to another closed ring.

"Fused ring" refers to fused aryl or cyclyl ring. For example, about six or less, about five or less, about four or less, about three or less, or about two rings can be fused. Each ring can be independently selected from the group consisting of aryl, heteroaryl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl rings, each of which ring may independently be substituted or unsubstituted, having about four to about ten, about four to about thirteen, or about four to about fourteen ring atoms.

The number of rings in a small molecule refers to the number of single or fused ring systems. Thus, for example a fused ring can be considered to be one ring. As non-limiting examples, a phenyl ring, naphthalene, and norbomane, for purposes of the present invention, are all considered to be one ring, whereas biphenyl, which is not fused, is considered to be two rings.

A "heteroatom" refers to N, O, S, or P. In some embodiments, heteroatom refers to N, O, or S, where indicated. Heteroatoms shall include any oxidized form of nitrogen, sulfur, and phosphorus and the quaternized form of any basic nitrogen.

Accordingly, examples of small molecule ring systems are:

"Aryl", used alone or as part of a larger moiety as in "aralkyl", refers to aromatic rings having six ring carbon atoms.

"Fused aryl," refers to fused about two to about three aromatic rings having about six to about ten, about six to about thirteen, or about six to about fourteen ring carbon atoms.

"Fused heteroaryl" refers to fused about two to about three heteroaryl rings wherein at least one of the rings is a heteroaryl, having about five to about ten, about five to about thirteen, or about five to about fourteen ring atoms.

"Fused cycloalkyl" refers to fused about two to about three cycloalkyl rings having about four to about ten, about four to about thirteen, or about four to about fourteen ring carbon atoms.

"Fused heterocycloalkyl" refers to fused about two to about three heterocycloalkyl rings, wherein at least one of the rings is a heterocycloalkyl, having about four to about ten, about four to about thirteen, or about four to about fourteen ring atoms.

"Heterocycloalkyl" refers to cycloalkyls comprising one or more heteroatoms in place of a ring carbon atom.

"Lower heterocycloalkyl" refers to cycloalkyl groups containing about three to six ring members.

"Heterocycloalkenyl" refers to cycloalkenyls comprising one or more heteroatoms in place of a ring carbon atom. "Lower heterocycloalkenyl" refers to cycloalkyl groups containing about three to about six ring members. The term "heterocycloalkenyl" does not refer to heteroaryls.

"Heteroaryl" refers to aromatic rings containing about three, about five, about six, about seven, or about eight ring atoms, comprising carbon and one or more heteroatoms.

"Lower heteroaryl" refers to heteroaryls containing about three, about five, or about

six ring members.

Examplery preferred scaffold structures can e.g. be selected from the group consisting of quinazoline, tricyclic quinazoline, purine, pyrimidine, phenylamine-pyrimidine, phthalazine, benzylidene malononitrile, amino acid, tertiary amine, peptide, lactam, sultam, lactone, pyrrole, pyrrolidine, pyrrolinone, oxazole, isoxazole, oxazoline, isoxazoline, oxazolinone, isoxazolinone, thiazole, thiozolidinone, hydantoin, pyrazole, pyrazoline, pyrazolone, imidazole, imidazolidine, imidazolone, triazole, thiadiazole, oxadiazole, benzoffuran, isobenzofuran, dihydrobenzofuran, dihydroisobenzofuran, indole, indoline, benzoxazole, oxindole, indolizine, benzimidazole, benzimidazolone, pyridine, piperidine, piperidinone, pyrimidinone, piperazine, piperazinone, diketopiperazine, metathiazanone, morpholine, thiomorpholine, phenol, dihydropyran, quinoline, isoquinoline, quinolinone, isoquinolinone, quinolone, quinazolinone, quinoxalinone, benzopiperazinone, quinazolinedione, benzazepine and azepine.

Further exemplary scaffold structures linked to the display oligonucleotides are selected from the group consisting of:

hydrido,

substituted and unsubstituted alkyl, substituted and unsubstituted haloalkyl, substituted and unsubstituted hydroxyalkyl, substituted and unsubstituted alkylsulfonyl,

substituted and unsubstituted alkenyl,

halo,

substituted and unsubstituted alkoxy, substituted and unsubstituted alkoxyalkyl, substituted and unsubstituted haloalkoxy, substituted and unsubstituted haloalkoxyalkyl,

substituted and unsubstituted aryl,

substituted and unsubstituted heterocyclic,

substituted and unsubstituted heteroaryl,

sulfonyl, substituted and unsubstituted alkylsulfonyl, substituted and unsubstituted arylsulfonyl, sulfamyl, sulfonamidyl, aminosulfonyl, substituted and unsubstituted N-alkylaminosulfonyl, substituted and unsubstituted N-arylaminosulfonyl, substituted and unsubstituted N,N-dialkylaminosulfonyl, substituted and unsubstituted N-alkyl-N-arylaminosulfonyl, substituted and unsubstituted N-alkylaminosulfonyl, substituted and unsubstituted N,N-dialkylaminosulfonyl, substituted and unsubstituted N-arylaminosulfonyl, substituted and unsubstituted N-alkyl-N-arylaminosulfonyl,

carboxy, substituted and unsubstituted carboxyalkyl,

carbonyl, substituted and unsubstituted alkylcarbonyl, substituted and unsubstituted alkylcarbonylalkyl,

substituted and unsubstituted alkoxycarbonyl, substituted and unsubstituted alkoxycarbonylalkyl,

aminocarbonyl, substituted and unsubstituted aminocarbonylalkyl, substituted and unsubstituted N-alkylaminocarbonyl, substituted and unsubstituted N-arylaminocarbonyl, substituted and unsubstituted N,N-dialkylaminocarbonyl, substituted and unsubstituted N-alkyl-N-arylaminocarbonyl, substituted and unsubstituted N-alkyl-N-hydroxyaminocarbonyl, substituted and unsubstituted N-alkyl-N-hydroxyaminocarbonylalkyl, substituted and unsubstituted N-alkylaminocarbonyl, substituted and unsubstituted N,N-dialkylaminocarbonyl, substituted and unsubstituted N-arylaminocarbonyl, substituted and unsubstituted N-alkyl-N-arylaminocarbonyl, substituted and unsubstituted aminocarbonylalkyl, substituted and unsubstituted N-cycloalkylaminocarbonyl,

substituted and unsubstituted aminoalkyl, substituted and unsubstituted alkylaminoalkyl,

amidino,

cyanoamidino,

substituted and unsubstituted heterocyclicalkyl,

substituted and unsubstituted aralkyl,

substituted and unsubstituted cycloalkyl,

substituted and unsubstituted cycloalkenyl,

substituted and unsubstituted alkylthio,

substituted and unsubstituted alkylsulfinyl,

substituted and unsubstituted N-alkylamino, substituted and unsubstituted N,N-dialkylamino,

substituted and unsubstituted arylamino, substituted and unsubstituted aralkylamino, substituted and unsubstituted N-alkyl-N-arylamino, substituted and unsubstituted N-aralkyl-N-alkylamino, substituted and unsubstituted N-arylaminoalkyl, substituted and unsubstituted N-aralkylaminoalkyl, substituted and unsubstituted N-alkyl-N-arylaminoalkyl, substituted and unsubstituted N-aralkyl-N-alkylaminoalkyl,

acyl, acylamino,

substituted and unsubstituted arylthio, substituted and unsubstituted aralkylthio,

substituted and unsubstituted aryloxy, substituted and unsubstituted aralkoxy,

substituted and unsubstituted haloaralkyl,

substituted and unsubstituted carboxyhaloalkyl,

substituted and unsubstituted alkoxycarbonylhaloalkyl, substituted and unsubstituted aminocarbonylhaloalkyl, substituted and unsubstituted alkylaminocarbonylhaloalkyl,

substituted and unsubstituted alkoxycarbonylcyanoalkenyl,

substituted and unsubstituted carboxyalkylaminocarbonyl,

substituted and unsubstituted aralkoxycarbonylalkylaminocarbonyl,

substituted and unsubstituted cycloalkylalkyl, and

substituted and unsubstituted aralkenyl.

The same or different scaffolds comprising a plurality of sites for functionalization react with one or more identical or different reactants in order to generate a compound library comprising different small molecules. As used herein, the term "scaffold reactive group" refers to a chemical moiety that is capable of reacting with the reactive group of a reactant or chemical entity during the synthesis if the small molecule. Preferred scaffold reactive groups include, but are not limited to, hydroxyl, carboxyl, amino, thiol, aldehyde, halogen, nitro, cyano, amido, urea, carbonate, carbamate, isocyanate, sulfone, sulfonate, sulfonamide, sulfoxide, amino acid, aryl, cycloalkyl, heterocyclyl, heteroaryl, etc. One of skill in the art will be aware of other common functional groups that are encompassed by the present invention.

As used herein, the term "chemical entity reactive group" refers to a chemical moiety of a reactant capable of reacting with one or more scaffold reactive groups. Preferred reactive groups of a reactant include, but are not limited to, hydroxyl, carboxyl, amino, thiol, aldehyde, halogen, nitro, cyano, amido, urea, carbonate, carbamate, isocyanate, sulfone, sulfonate, sulfonamide, sulfoxide, amino acid, aryl, cycloalkyl, heterocyclyl, heteroaryl, etc. One of skill in the art will be aware of other common functional groups that are encompassed by the present invention.

The small molecule compounds of the present invention can be prepared using a variety of synthetic reactions. Suitable reaction chemistries are preferably selected from the following group: Amine acylation, reductive alkylation, aromatic reduction, aromatic acylation, aromatic cyclization, aryl-aryl coupling, [3+2] cycloaddition, Mitsunobu reaction, nucleophilic aromatic substitution, sulfonylation, aromatic halide displacement, Michael addition, Wittig reaction, Knoevenagel condensation, reductive amination, Heck reaction, Stille reaction, Suzuki reaction, Aldol

condensation, Claisen condensation, amino acid coupling, amide bond formation, acetal formation, Diels-Alder reaction, [2+2] cycloaddition, enamine formation, esterification, Friedel Crafts reaction, glycosylation, Grignard reaction, Homer-Emmons reaction, hydrolysis, imine formation, metathesis reaction, nucleophilic substitution, oxidation, Pictet-Spengler reaction, Sonogashira reaction, thiazolidine formation, thiourea formation and urea formation.

Accordingly, the reactants and scaffolds of the present invention are those that enable the reactions above to occur. These include, but are not limited to, nucleophiles, electrophiles, acylating agents, aldehydes, carboxylic acids, alcohols, nitro, amino, carboxyl, aryl, heteroaryl, heterocyclyl, boronic acids, phosphorous ylides, etc. One of skill in the art can envision other synthetic reactions and reactive components useful in the present invention.

Figure 58 highlights several reactions that can be used to prepare the small molecule compounds of the present invention, and the corresponding coding reactions and reactive components. In figure 58, one of skill in the art will understand that radicals R, R_1 and R_2 can be any of the above described groups, such as, for example, hydrogen, alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, all optionally substituted as disclosed herein above. One of skill in the art will further understand that radical Ar is an aryl, which can be, for example, phenyl, naphthyl, pyridyl and thienyl. In addition, one of skill in the art will understand that radical X can be, for example, hydrogen, halogen alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl.

Contacting a scaffold with one or more reactants results in the conversion of the scaffold into a small molecule, or an intermediate scaffold structure to be further reacted or modified.

Accordingly, in one embodiment of the present invention, reactants comprising one or more reactive groups, react with one or more, preferably more, such as 2, 3, 4, 5, 6, 7, 8, 9, 10, or from 10 to 20, reactive groups of a scaffold comprising a plurality of such reactive groups, by one or more reactions selected from the group consisting of amine acylation, reductive alkylation, aromatic reduction, aromatic acylation, aromatic cyclization, aryl-aryl coupling, [3+2] cycloaddition, Mitsunobu reaction, nucleophilic aromatic substitution, sulfonylation, aromatic halide displacement,

Michael addition, Wittig reaction, Knoevenagel condensation, reductive amination, Heck reaction, Stille reaction, Suzuki reaction, Aldol condensation, Claisen condensation, amino acid coupling, amide bond formation, acetal formation, Diels-Alder reaction, [2+2] cycloaddition, enamine formation, esterification, Friedel Crafts reaction, glycosylation, Grignard reaction, Homer-Emmons reaction, hydrolysis, imine formation, metathesis reaction, nucleophilic substitution, oxidation, Pictet-Spengler reaction, Sonogashira reaction, thiazolidine formation, thiourea formation and urea formation, wherein said scaffold preferably comprises a structural component selected from the group consisting of a cyclic or bicyclic hydrocarbon, a steroid, a sugar, a heterocyclic structure, a polycyclic aromatic molecule, an amine, an amino acid, a multi-functional small molecule, a peptide or a polymer having various substituents at defined positions.

Suitable scaffolds of the present invention include, but are not limited to, quinazoline, tricyclic quinazoline, purine, pyrimidine, phenylamine-pyrimidine, phthalazine, benzylidene malononitrile, amino acid, tertiary amine, peptide, polymer, aromatic compounds containing ortho-nitro fluoride(s), aromatic compounds containing para-nitro fluoride(s), aromatic compounds containing ortho-nitro chloromethyl, aromatic compounds containing ortho-nitro bromomethyl, lactam, sultam, lactone, pyrrole, pyrrolidine, pyrrolinone, oxazole, isoxazole, oxazoline, isoxazoline, oxazolinone, isoxazolinone, thiazole, thiozolidinone, hydantoin, pyrazole, pyrazoline, pyrazolone, imidazole, imidazolidine, imidazolone, triazole, thiadiazole, oxadiazole, benzofuran, isobenzofuran, dihydrobenzofuran, dihydroisobenzofuran, indole, indoline, benzoxazole, oxindole, indolizine, benzimidazole, benzimidazolone, pyridine, piperidine, piperidinone, pyrimidinone, piperazine, piperazinone, diketopiperazine, metathiazanone, morpholine, thiomorpholine, phenol, dihydropyran, quinoline, isoquinoline, quinolinone, isoquinolinone, quinolone, quinazolinone, quinoxalinone, benzopiperazinone, quinazolinedione, benzazepine and azepine, and wherein said scaffold preferably comprises at least two scaffold reactive groups selected from the group consisting of hydroxyl, carboxyl, amino, thiol, aldehyde, halogen, nitro, cyano, amido, urea, carbonate, carbamate, isocyanate, sulfone, sulfonate, sulfonamide, sulfoxide, etc., for reaction with said one or more reactants.

The compound libraries can be partitioned or enriched with the selection of possible "lead candidates" or "drug candidates" as a result. The identification of "lead

candidates" or "drug candidates" typically result when an association is formed between a small molecule member of the compound library and a target compound.

A "library" is a collection of library compounds, such as a collection of different small molecules. The library can be virtual, in that it is an in silico or electronic collection of structures used for computational analysis as described herein. The library is preferably physical, in that the set of small molecules are synthesized, isolated, or purified.

A "lead candidate" is a library compound, such as a small molecule, that binds to a biological target molecule and is designed to modulate the activity of a target protein. A lead candidate can be used to develop a drug candidate, or a drug to be used to treat a disorder or disease in an animal, including, for example, by interacting with a protein of said animal, or with a bacterial, viral, fungal, or other organism that can be implicated in said animal disorder or disease, and that is selected for further testing either in cells, in animal models, or in the target organism. A lead candidate may also be used to develop compositions to modulate plant diseases or disorders, including, for example, by modulating plant protein activity, or by interacting with a bacterial, viral, fungal, or other organism implicated in said disease or disorder.

A "drug candidate" is a lead candidate that has biological activity against a biological target molecule and has ADMET (absorption, distribution, metabolism, excretion and toxicity) properties appropriate for it to be evaluated in an animal, including a human, clinical studies in a designated therapeutic application.

A "compound library" is a group comprising more than one compound, such as more than one different small molecule, used for drug discovery. The compounds in the library can be small molecules designed to be linked to other compounds or small molecules, or the compounds can be small molecules designed to be used without linkage to other small molecules.

A "plurality" is more than one of whatever noun "plurality" modifies in the sentence.

The term "obtain" refers to any method of obtaining, for example, a small molecule, a library of such different small molecules, or a target molecule. The method used to

obtain such compounds, biological target molecules, or libraries, may comprise synthesis, purchase, or any means the compounds, biological target molecules, or libraries can be obtained.

By "activity against" is meant that a compound may have binding activity by binding to a biological target molecule, or it may have an effect on the enzymatic or other biological activity of a target, when present in a target activity assay. Biological activity and biochemical activity refer to any in vivo or in vitro activity of a target biological molecule. Non-limiting examples include the activity of a target molecule in an in vitro, cellular, or organism level assay. As a non-limiting example with an enzymatic protein as the target molecule, the activity includes at least the binding of the target molecule to one or more substrates, the release of a product or reactant by the target molecule, or the overall catalytic activity of the target molecule. These activities can be accessed directly or indirectly in an in vitro or cell based assay, or alternatively in a phenotypic assay based on the effect of the activity on an organism. As a further non-limiting example wherein the target molecule is a kinase, the activity includes at least the binding of the kinase to its target polypeptide and/or other substrate (such as ATP as a non-limiting example) as well as the actual activity of phosphorylating a target polypeptide.

Obtaining a crystal of a biological target molecule in association with or in interaction with a test small molecule includes any method of obtaining a compound in a crystal, in association or interaction with a target protein. This method includes soaking a crystal in a solution of one or more potential compounds, or ligands, or incubating a target protein in the presence of one or more potential compounds, or ligands.

By "or" is meant one, or another member of a group, or more than one member. For example, A, B, or C, may indicate any of the following: A alone; B alone; C alone; A and B; B and C; A and C; A, B, and C.

"Association" refers to the status of two or more molecules that are in close proximity to each other. The two molecules can be associated non-covalently, for example, by hydrogen-bonding, van der Waals, electrostatic or hydrophobic interactions, or covalently.

"Active Site" refers to a site in a target protein that associates with a substrate for target protein activity. This site may include, for example, residues involved in catalysis, as well as residues involved in binding a substrate. Inhibitors may bind to the residues of the active site.

"Binding site" refers to a region in a target protein, which, for example, associates with a ligand such as a natural substrate, non-natural substrate, inhibitor, substrate analog, agonist or antagonist, protein, co-factor or small molecule, as well as, optionally, in addition, various ions or water, and/or has an internal cavity sufficient to bind a small molecule and can be used as a target for binding drugs. The term includes the active site but is not limited thereby.

"Crystal" refers to a composition comprising a biological target molecule, including, for example, macromolecular drug receptor targets, including protein, including, for example, but not limited to, polypeptides, and nucleic acid targets, for example, but not limited to, DNA, RNA, and ribosomal subunits, and carbohydrate targets, for example, but not limited to, glycoproteins, crystalline form. The term "crystal" includes native crystals, and heavy-atom derivative crystals, as defined herein. The discussion below often uses a target protein as a exemplary, and non-limiting example. The discussion applies in an analogous manner to all possible target molecules.

"Alkyl" and "alkoxy" used alone or as part of a larger moiety refers to both straight and branched chains containing about one to about eight carbon atoms. "Lower alkyl" and "lower alkoxy" refer to alkyl or alkoxy groups containing about one to about four carbon atoms.

"Cyclyl", "cycloalkyl", or "cycloalkenyl" refer to cyclic alkyl or alkenyl groups containing from about three to about eight carbon atoms. "Lower cyclyl," "lower cycloalkyl." or "lower cycloalkenyl" refer to cyclic groups containing from about three to about six carbon atoms.

"Alkenyl" and "alkynyl" used alone or as part of a larger moiety shall include both straight and branched chains containing about two to about eight carbon atoms, with one or more unsaturated bonds between carbons. "Lower alkenyl" and "lower alkynyl" include alkenyl and alkynyl groups containing from about two to about five

carbon atoms.

"Halogen" means F, Cl, Br, or I.

"Linker group" of a bifunctional complex means an organic moiety that connects two parts of the bifunctional complex, typically the small molecule and the oligonucleotide identifier. Linkers are typically comprised of an atom such as oxygen or sulfur, a unit such as --NH-- or --CH_2--, or a chain of atoms, such as an alkylidene chain. The molecular mass of a linker is typically in the range of about 14 to about 200. Examples of linkers are known to those of ordinary skill in the art and include, but are not limited to, a saturated or unsaturated C_{1-6} alkylidene chain which is optionally substituted, and wherein up to two saturated carbons of the chain are optionally replaced by --C(=O)--, --CONH--, CONHNH--, --CO_2--, --$NHCO_2$--, --O--, --NHCONH--, --O(C=O)--, --O(C=O)NH--, --NHNH--, --NHCO--, --S--, --SO--, --SO_2--, --NH--, --SO_2NH--, or $NHSO_2$--.

An LogP value can be, for example, a calculated Log P value, for example, one determined by a computer program for predicting Log P, the log of the octanol-water partition coefficient commonly used as an empirical descriptor for predicting bioavailability (e.g. Lipinski's Rule of 5; Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. (1997) Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv. Drug Delivery Rev. 23, 3-25). The calculated logP value may, for example, be the SlogP value. SlogP is implemented in the MOE software suite from Chemical Computing Group, www.chemcomp.com. SlogP is based on an atomic contribution model (Wildman, S. A., Crippen, G. M.; Prediction of Physicochemical Parameters by Atomic Contributions; J. Chem. Inf. Comput. Sci., 39(5), 868-873 (1999)).

<u>Linker moiety of a bifunctional complex</u>

The nascent bifunctional complex comprising a chemical reaction site and a priming site for enzymatic addition of a tag can also comprise a linking moiety connecting the chemical reaction site and the priming site.

In some embodiments it is preferable that the linker ensures that a reactive group or a building block (reactant) or an encoded molecule is spaced away from the tag. In some embodiments it is also preferable that the linker ensures that a reactive group,

a building block (reactant) or an encoded molecule can efficiently interact with another object such as a target used for screening/affinity selection.

The linker may be composed of one or more atoms. The linker may include monomer units such as a peptide, protein, carbohydrates and substituted carbohydrates, a nucleotide, or any unit synthesized using organic and/or inorganic chemistry such as ethylenglycol; 1,3-propylenglycol; 1,4-propylenglycol; 1,5-pentylenglycol. Any unit may be in substituted form, e.g., 1,3.propylenglycol hydroxyl-substituted at the 2 position (Propane-1,2,3-triol). The linker may also include a polymer such as an organic polymer, e.g. a polyethylenglycol, a polypeptide, or an oligonucleotide, polyvinyl, acetylene or polyacetylene, aryl/hetaryl and substituted aryl/hetaryl, ethers and polyethers such as e.g. polyethylenglycol and substituted polyethers, amines, polyamines and substituted polyamines, single- or double-stranded oligonucleotides, and polyamides and natural and unnatural polypeptides. The linker may contain any combination of monomeric and polymeric units. The linker may also contain branching units. The linker may be flexible or rigid and contain flexible and/or rigid parts. The linker may be attached to one or more reactive groups by one or more atoms. Moreover, the linker may contain one or more reactive groups. The linker may be attached to the tag via one or more atoms, e.g. via a phosphate group.
The attachment point may be anywhere on the tags such as a 5' or 3' phosphate, a 5' or 3' OH, carbon, oxygen or nitrogen on one or more nucleotides. The linker may be attached one or more tags such as both strands of a double stranded tag.The linker may be attached to the tag by one or more covalent bonds and/or one or more noncovalent bonds, e.g. the linker may include a biotin moiety which can bind noncovalently to a streptavidin molecule attached to the tag. Preferably the length of the linker is in the range of 1-50 angstrom, more preferably 5-30 angstrom, most preferably 10-25 angstrom. Preferably, the linker separates the linker-tag attachment point from a reactive group by 5-50 atomic bonds, more preferably, by 10-30 atomic bonds, most preferably by 15-25 atomic bonds. Preferably, the linker is prepared from Diisopropyl-phosphoramidous acid 2-cyano-ethyl ester 2-[2-(2-{2-[2-(2-{[(4-methoxy-phenyl)-diphenyl-methyl]-amino}-ethoxy)-ethoxy]-ethoxy}-ethoxy)-ethoxy]-ethyl ester or similar compound. Preferably, the linker contains the structure 2-[2-(2-{2-[2-(2-Amino-ethoxy)-ethoxy]-ethoxy}-ethoxy)-ethoxy]-ethanol.

Cleavable linkers can be cleaved in any number of ways, e.g., by photolysis or increased temperature, or by the addition of acid, base, enzymes, ribozymes, other catalysts, or any other agents.

To maintain a physical link between the identifier and the encoded molecule (in the case of stage 2 synthesis, the template and the encoded molecule), at least one non-cleavable linker is needed. The non-cleavable linker may of course be cleavable under certain conditions, but is non-cleavable under the conditions that lead to the bi-functional molecule employed in the screening. This non-cleavable linker is preferably flexible, enabling it to expose the encoded molecule in an optimal way.

Under certain conditions it may desirable to be able to cleave the linker before, during or after the screening of the library has been done, for example in order to perform a mass spectrometric analysis of the encoded molecule without the identifier attached, or to perform other types of assays on the free encoded molecule.

The linking moiety in one embodiment separates the priming site from the chemical reaction site so as to allow an enzyme to perform the tag addition and provide for a hybridisation region. The linking moiety can be a nucleic acid sequence, such as an oligonucleotide. The length of the oligonucleotide is preferably suitable for hybridisation with a complementing oligonucleotide, i.e. the number of nucleotides in the linking moiety is suitably 2 or more, such as 3 or more, for example 4 or above, such as 5 or more, for example 6 or more, such as 7 or more, for example 8 or more nucleotides.

In a certain embodiment, the linking moiety is attached to the chemical reaction site via a spacer comprising a selectively cleavable linker to enable release of the molecule from the identifier oligonucleotide in a step subsequent to the formation of the final bifunctional complex. The cleavable linker can be selectively cleavable, i.e. conditions can be selected that only cleave that particular linker.

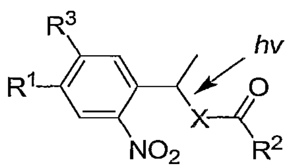
The cleavable linkers can be selected from a variety chemical structures. Examples of linkers includes, but are not limited to, linkers having an enzymatic cleavage site,

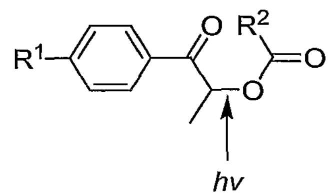
linkers comprising a chemical degradable component, linkers cleavable by electromagnetic radiation.

Examples of linkers cleavable by electromagnetic radiation (light)

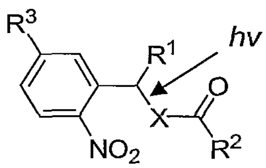
o-nitrobenzyl

p-alkoxy



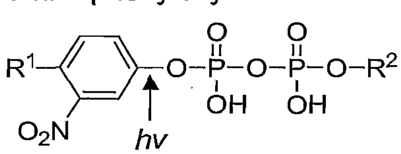


o-nitrobenzyl in exo position



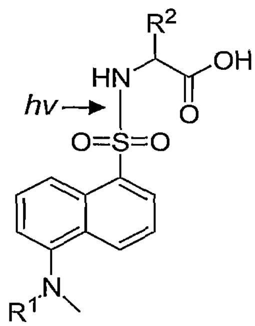
For more details see Holmes CP. J. Org. Chem. **1997,** *62*, 2370-2380

3-nitrophenyloxy



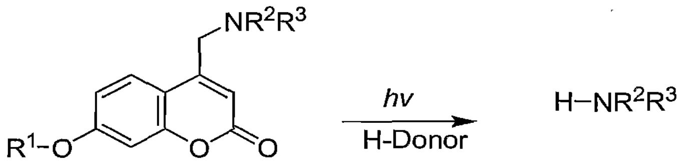
For more details see Rajasekharan Pillai, V. N. Synthesis. **1980**, 1-26

Dansyl derivatives:



For more details see Rajasekharan Pillai, V. N. Synthesis. **1980**, 1-26

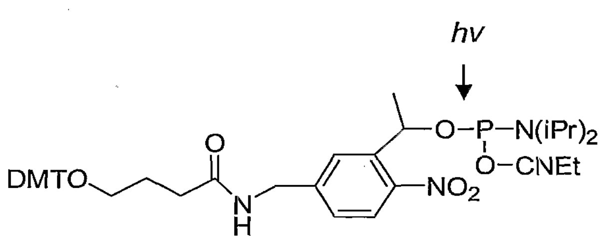
Coumarin derivatives



For more details see R. O. Schoenleber, B. Giese. Synlett **2003**, 501-504

R^1 and R^2 can be any molecule or chemical entity (CE) such as those exemplified herein above under section A (acylation reactions), respectively. Moreover, R^1 and R^2 can be either the target or a solid support, respectively. R^3 can be e.g. H or OCH_3 independently of R^1 and R^2. If X is O then the product will be a carboxylic acid. If X is NH the product will be a carboxamide

One specific example is the PC Spacer Phosphoramidite (Glen research catalog # 10-4913-90) which can be introduced in an oligonucleotide during synthesis and cleaved by subjecting the sample in water to UV light (~ 300-350 nm) for 30 seconds to 1 minute.

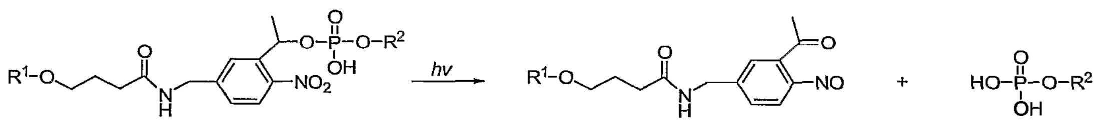


DMT = 4,4'-Dimethoxytrityl

iPr = Isopropyl

CNEt = Cyanoethyl

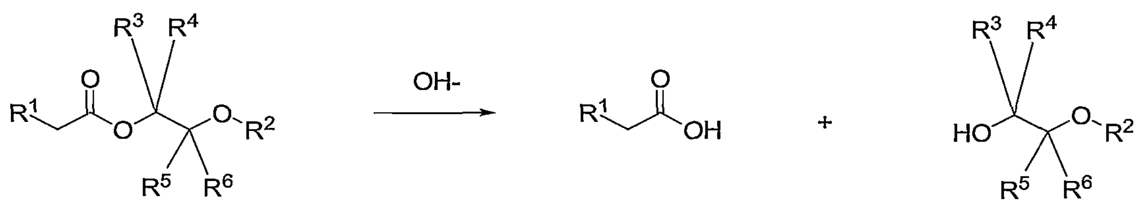
The above PC spacer phosphoamidite is suitable incorporated in a library of complexes at a position between the indentifier and the potential drug candidate. The spacer can be cleaved according to the following reaction.



R^1 and R^2 can be any molecule or chemical entity (CE) such as those exemplified herein above under section A (acylation reactions). Moreover, R^1 and R^2 can be either the target or a solid support, respectively. In a preferred aspect R^2 is an oligonucleotide identifier and the R^1 is the molecule. When the linker is cleaved a phosphate group is generated allowing for further biological reactions. As an example, the phosphate group can be positioned in the 5´end of an oligonucleotide allowing for an enzymatic ligation process to take place.

<u>Examples of linkers cleavable by chemical agents</u>:

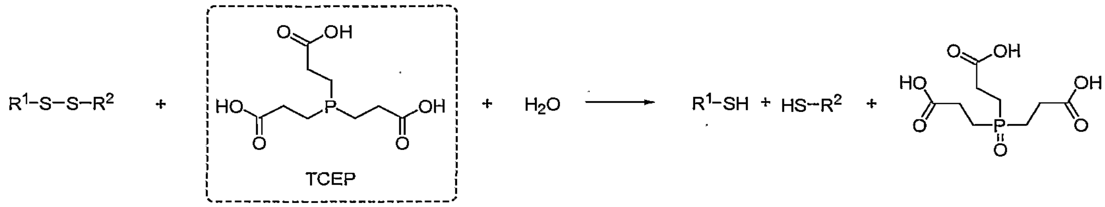
Ester linkers can be cleaved by nucleophilic attack using e.g. hydroxide ions. In practice this can be accomplished by subjecting the target-ligand complex to a base for a short period.



R^1 and R^2 can be the either of be the potential drug candidate or the identifier, respectively. R^{4-6} can be any of the following: H, CN, F, NO_2, SO_2NR_2.

Disulfide linkers can efficiently be cleaved / reduced by Tris (2-carboxyethyl) phosphine (TCEP). TCEP selectively and completely reduces even the most stable water-soluble alkyl disulfides over a wide pH range. These reductions frequently

required less than 5 minutes at room temperature. TCEP is a non-volatile and odorless reductant and unlike most other reducing agents, it is resistant to air oxidation. Trialkylphosphines such as TCEP are stable in aqueous solution, selectively reduce disulfide bonds, and are essentially unreactive toward other functional groups commonly found in proteins.



More details on the reduction of disulfide bonds can be found in Kirley, T.L.(1989), Reduction and fluorescent labeling of cyst(e)ine-containing proteins for subsequent structural analysis, *Anal. Biochem.* **180**, 231 and Levison, M.E., *et al.* (1969), Reduction of biological substances by water-soluble phosphines: Gamma-globulin. *Experentia* **25**, 126-127.

Linkers cleavable by enzymes

The linker connecting the potential drug candidate with the identifier or the solid support and the target can include a peptide region that allows a specific cleavage using a protease. This is a well-known strategy in molecular biology. Site-specific proteases and their cognate target amino acid sequences are often used to remove the fusion protein tags that facilitate enhanced expression, solubility, secretion or purification of the fusion protein.

Various proteases can be used to accomplish a specific cleavage. The specificity is especially important when the cleavage site is presented together with other sequences such as for example the fusion proteins. Various conditions have been optimized in order to enhance the cleavage efficiency and control the specificity. These conditions are available and know in the art.

Enterokinase is one example of an enzyme (serine protease) that cut a specific amino acid sequence. Enterokinase recognition site is Asp-Asp-Asp-Asp-Lys (DDDDK), and it cleaves C-terminally of Lys. Purified recombinant Enterokinase is commercially available and is highly active over wide ranges in pH (pH 4.5-9.5) and

temperature (4-45°C).

The nuclear inclusion protease from tobacco etch virus (TEV) is another commercially available and well-characterized proteases that can be used to cut at a specific amino acid sequence. TEV protease cleaves the sequence Glu-Asn-Leu-Tyr-Phe-Gln-Gly/Ser (ENLYFQG/S) between Gln-Gly or Gln-Ser with high specificity.

Another well-known protease is thrombin that specifically cleaves the sequence Leu-Val-Pro-Arg-Gly-Ser (LVPAGS) between Arg-Gly. Thrombin has also been used for cleavage of recombinant fusion proteins. Other sequences can also be used for thrombin cleavage; these sequences are more or less specific and more or less efficiently cleaved by thrombin. Thrombin is a highly active protease and various reaction conditions are known to the public.

Activated coagulation factor FX (FXa) is also known to be a specific and useful protease. This enzyme cleaves C-terminal of Arg at the sequence Ile-Glu-Gly-Arg (IEGR). FXa is frequently used to cut between fusion proteins when producing proteins with recombinant technology. Other recognition sequences can also be used for FXa.

Other types of proteolytic enzymes can also be used that recognize specific amino acid sequences. In addition, proteolytic enzymes that cleave amino acid sequences in an un-specific manner can also be used if only the linker contains an amino acid sequence in the complex molecule.

Other type of molecules such as ribozymes, catalytically active antibodies, or lipases can also be used. The only prerequisite is that the catalytically active molecule can cleave the specific structure used as the linker, or as a part of the linker, that connects the encoding region and the displayed molecule or, in the alternative the solid support and the target. Also, a variety of endonucleases are available that recognize and cleave a double stranded nucleic acid having a specific sequence of nucleotides.

Molecules

A molecule can be formed by the reaction of one or more reactive groups on one or more reactants or a molecule can be formed by the reaction of one or more reactive groups on one or more reactants and one or more chemical reaction sites.

A molecule can comprise one or more atoms and one or more bonds, wherein such bonds between atoms may optionally be single bonds, double bonds or triple bonds and a combination thereof, wherein such atoms may comprise carbon, silicon, nitrogen, phosphorous, oxygen, sulfur, selenium, fluorine, chlorine, bromine, iodine, borane, stannane, lithium, sodium, potassium, kalium, calcium, barium, strontium, including any combination thereof. In further embodiments, a molecule may comprise other atoms in the periodic system.

In one or more embodiments, a reactive group may comprise one or more atoms and one or more bonds, wherein such bonds between atoms may optionally be single bonds, double bonds or triple bonds and a combination thereof, wherein such atoms may comprise carbon, silicon, nitrogen, phosphorous, oxygen, sulfur, selenium, fluorine, chlorine, bromine, iodine, borane, stannane, lithium, sodium, potassium, kalium, calcium, barium, strontium. In further embodiments, a molecule may comprise other atoms in the periodic system.

In one or more embodiments, a chemical reaction site may comprise one or more atoms and one or more bonds, wherein such bonds between atoms may optionally be single bonds, double bonds or triple bonds and a combination thereof, wherein such atoms may comprise carbon, silicon, nitrogen, phosphorous, oxygen, sulfur, selenium, fluorine, chlorine, bromine, iodine, borane, stannane, lithium, sodium, potassium, kalium, calcium, barium, strontium. In further embodiments, a molecule may comprise other atoms in the periodic system.

In one or more embodiments, the molecule comprisings the molecule, which can be formed following the reaction of one or more reactants with one or more chemical reaction sites, where the molecule is linked through a linker to a display oligonucleotide optionally covalently linked to one or more tags.

In one or more embodiments, the molecule comprisings the chemical motif formed by reaction of reactive groups comprising atoms participating in the reaction

between one or more reactive groups on one or more reactants and one or more chemical reaction sites.

In one embodiment, the molecule comprisings a carboxamide. In another embodiment, the molecule comprisings a sulfonamide. In a further embodiment, the molecule comprisings a urea group. In further embodiments, the molecule comprisings an amine. In another embodiment, the molecule comprisings an ether. In a further embodiment, the molecule comprisings an ester for example an carboxylic acid ester. In a further embodiment, the molecule comprisings an alkene. In a further embodiment, the molecule comprisings an alkyne. In a further embodiment, the molecule comprisings an alkane. In a further embodiment, the molecule comprisings a thioether. In a further embodiment, the molecule comprisings a sulfone. In a further embodiment, the molecule comprisings a sulfoxide. In a further embodiment, the molecule comprisings a sulfonamide. In a further embodiment, the molecule comprisings a carbamate. In a further embodiment, the molecule comprisings a carbonate. In a further embodiment, the molecule comprisings a 1,2-diol. In a further embodiment, the molecule comprisings a 1,2-dioxoalkane. In a further embodiment, the molecule comprisings a ketone. In a further embodiment, the molecule comprisings an imine. In a further embodiment, the molecule comprisings a hydrazone. In a further embodiment, the molecule comprisings an oxime. In a further embodiment, the molecule comprisings an aminohetarene.

In one embodiment the molecule comprising a cyclic structure such as a 3-40 member ring, such as for example an 18-40 member ring, such as for example a 3-7 member ring, for example an 8-24 member ring, for example an 8-18 member ring, for example an 8-14 member ring, for example a 5-7 member ring, such as for example a 3 member ring, for example a 4 member ring, for example a 5 member ring, for example a 6 member ring, for example a 7 member ring, for example an 8 member ring, for example a 9 member ring, for example a 10 member ring, for example an 11 member ring, for example a 12 member ring, for example a 13 member ring, for example a 14 member ring, for example a 15 member ring, for example a 16 member ring, for example a 17 member ring, for example an 18 member ring.

In one embodiment the molecule comprisings a cyclic structure, for example an aliphatic ring, for example an aromatic ring, for example a partially unsaturated ring and a combination thereof.

In one embodiment the molecule comprising a 3 member ring comprising one or more carbon ring atoms and optionally one or more heteroatoms, for example one or more oxygen ring atoms, for example one or more nitrogen ring atoms, for example one or more sulfur ring atoms.

In one embodiment the molecule comprising a 4 member ring comprising one or more carbon ring atoms and optionally one or more heteroatoms, for example one or more oxygen ring atoms, for example one or more nitrogen ring atoms, for example one or more sulfur ring atoms.

In one embodiment the molecule comprising a 5 member ring comprising one or more carbon ring atoms and optionally one or more heteroatoms, for example one or more oxygen ring atoms, for example one or more nitrogen ring atoms, for example one or more sulfur ring atoms.

In one embodiment the molecule comprising a 6 member ring comprising one or more carbon ring atoms and optionally one or more heteroatoms, for example one or more oxygen ring atoms, for example one or more nitrogen ring atoms, for example one or more sulfur ring atoms.

In one embodiment the molecule comprising a 7 member ring comprising one or more carbon ring atoms and optionally one or more heteroatoms, for example one or more oxygen ring atoms, for example one or more nitrogen ring atoms, for example one or more sulfur ring atoms.

In one embodiment the molecule comprising an 8 member ring comprising one or more carbon ring atoms and optionally one or more heteroatoms, for example one or more oxygen ring atoms, for example one or more nitrogen ring atoms, for example one or more sulfur ring atoms.

In one embodiment the molecule comprising a 9 member ring comprising one or more carbon ring atoms and optionally one or more heteroatoms, for example one or more oxygen ring atoms, for example one or more nitrogen ring atoms, for example one or more sulfur ring atoms.

In one embodiment the molecule comprising a 10 member ring comprising one or more carbon ring atoms and optionally one or more heteroatoms, for example one or more oxygen ring atoms, for example one or more nitrogen ring atoms, for example one or more sulfur ring atoms.

In one embodiment the molecule comprising an 11 member ring comprising one or more carbon ring atoms and optionally one or more heteroatoms, for example one or more oxygen ring atoms, for example one or more nitrogen ring atoms, for example one or more sulfur ring atoms.
In one embodiment the molecule comprising a 12 member ring comprising one or more carbon ring atoms and optionally one or more heteroatoms, for example one or more oxygen ring atoms, for example one or more nitrogen ring atoms, for example one or more sulfur ring atoms.
In one embodiment the molecule comprising a 13 member ring comprising one or more carbon ring atoms and optionally one or more heteroatoms, for example one or more oxygen ring atoms, for example one or more nitrogen ring atoms, for example one or more sulfur ring atoms.
In one embodiment the molecule comprising a 14 member ring comprising one or more carbon ring atoms and optionally one or more heteroatoms, for example one or more oxygen ring atoms, for example one or more nitrogen ring atoms, for example one or more sulfur ring atoms.
In one embodiment the molecule comprising a 15 member ring comprising one or more carbon ring atoms and optionally one or more heteroatoms, for example one or more oxygen ring atoms, for example one or more nitrogen ring atoms, for example one or more sulfur ring atoms.
In one embodiment the molecule comprising a 16 member ring comprising one or more carbon ring atoms and optionally one or more heteroatoms, for example one or more oxygen ring atoms, for example one or more nitrogen ring atoms, for example one or more sulfur ring atoms.
In one embodiment the molecule comprising a 17 member ring comprising one or more carbon ring atoms and optionally one or more heteroatoms, for example one or more oxygen ring atoms, for example one or more nitrogen ring atoms, for example one or more sulfur ring atoms.
In one embodiment the molecule comprising an 18 member ring comprising one or more carbon ring atoms and optionally one or more heteroatoms, for example one or more oxygen ring atoms, for example one or more nitrogen ring atoms, for example one or more sulfur ring atoms.

In one embodiment a molecule comprises for example a fully unsaturated ring structure, for example a fully saturated ring structure, for example a partly saturated ring structure, wherein such ring structure may comprise a pyrrole, a

tetrahydrofuran, a tetrahydropyran, a furan, a thiophene, a pyrazole, an imidazole, a furazan, an oxazole, an isoxazole, a thiazole, an isothiazole, a 1,2,3-triazole, a 1,2,4-triazole, an 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole, a tetrazole, a pyridine, a pyridazine, a pyrimidine, a pyrazine, a piperidine, a piperazine, a morpholine, a thiomorpholine, an indole, an isoindole, an indazole, a purine, an indolizine, a purine, a quinoline, an isoquinoline, a quinazoline, a pteridine, a quinolizine, a carbazole, a phenazine, a phenothiazine, a phenanthridine, a chroman an oxolane, a dioxine, an aziridine, an oxirane, an azetidine, an azepine, which may optionally be substituted by one or more substituents.

In one embodiment a molecule comprises for example a fully unsaturated ring structure, for example a fully saturated ring structure, for example a partly saturated ring structure, wherein such ring structure may comprise a benzopyrrole, a benzotetrahydrofuran, a benzotetrahydropyran, a benzofuran, a benzothiophene, a benzopyrazole, an benzoimidazole, a benzofurazan, an benzooxazole, an benzoisoxazole, a benzothiazole, an benzoisothiazole, a benzo1,2,3-triazole, a benzopyridine, a benzopyridazine, a benzopyrimidine, a benzopyrazine, a benzopiperidine, a benzopiperazine, a benzomorpholine, a benzothiomorpholine, an benzoindole, an benzoisoindole, an benzoindazole, an benzoindolizine, a benzoquinoline, a benzoisoquinoline, a benzoquinazoline, a benzopteridine, a benzoquinolizine, a benzocarbazole, a benzophenazine, a benzophenothiazine, a benzophenanthridine, a benzochroman an benzooxolane, a benzodioxine, a benzoazetidine, a benzoazepine, which may optionally be substituted by one or more substituents.

In one embodiment a molecule comprises for example a fully unsaturated ring structure, for example a fully saturated ring structure, for example a partly saturated ring structure, wherein such ring structure may comprise a pyridopyrrole, a pyridotetrahydrofuran, a pyridotetrahydropyran, a pyridofuran, a pyridothiophene, a pyridopyrazole, an pyridoimidazole, a pyridofurazan, an pyridooxazole, an pyridoisoxazole, a pyridothiazole, an pyridoisothiazole, a pyrido1,2,3-triazole, a pyridopyridine, a pyridopyridazine, a pyridopyrimidine, a pyridopyrazine, a pyridopiperidine, a pyridopiperazine, a pyridomorpholine, a pyridothiomorpholine, an pyridoindole, an pyridoisoindole, an pyridoindazole, an pyridoindolizine, a pyridoquinoline, a pyridoisoquinoline, a pyridoquinazoline, a pyridopteridine, a pyridoquinolizine, a pyridocarbazole, a pyridophenazine, a pyridophenothiazine, a

pyridophenanthridine, a pyridochroman an pyridooxolane, a pyridodioxine, a pyridoazetidine, a pyridoazepine, which may optionally be substituted by one or more substituents.

In one embodiment a molecule comprises for example a fully unsaturated ring structure, for example a fully saturated ring structure, for example a partly saturated ring structure, wherein such ring structure may comprise a pyrrolopyrrole, a pyrrolotetrahydrofuran, a pyrrolotetrahydropyran, a pyrrolofuran, a pyrrolothiophene, a pyrrolopyrazole, an pyrroloimidazole, a pyrrolofurazan, an pyrrolooxazole, an pyrroloisoxazole, a pyrrolothiazole, an pyrroloisothiazole, a pyrrolo1,2,3-triazole, a pyrrolopyridine, a pyrrolopyridazine, a pyrrolopyrimidine, a pyrrolopyrazine, a pyrrolopiperidine, a pyrrolopiperazine, a pyrrolomorpholine, a pyrrolothiomorpholine, an pyrroloindole, an pyrroloisoindole, an pyrroloindazole, an pyrroloindolizine, a pyrroloquinoline, a pyrroloisoquinoline, a pyrroloquinazoline, a pyrrolopteridine, a pyrroloquinolizine, a pyrrolocarbazole, a pyrrolophenazine, a pyrrolophenothiazine, a pyrrolophenanthridine, a pyrrolochroman an pyrrolooxolane, a pyrrolodioxine, a pyrroloazetidine, a pyrroloazepine, which may optionally be substituted by one or more substituents.

In one embodiment a molecule comprises for example a fully unsaturated ring structure, for example a fully saturated ring structure, for example a partly saturated ring structure, wherein such ring structure may comprise a furopyrrole, a furotetrahydrofuran, a furotetrahydropyran, a furofuran, a furothiophene, a furopyrazole, an furoimidazole, a furofurazan, an furooxazole, an furoisoxazole, a furothiazole, an furoisothiazole, a furo1,2,3-triazole, a furopyridine, a furopyridazine, a furopyrimidine, a furopyrazine, a furopiperidine, a furopiperazine, a furomorpholine, a furothiomorpholine, an furoindole, an furoisoindole, an furoindazole, an furoindolizine, a furoquinoline, a furoisoquinoline, a furoquinazoline, a furopteridine, a furoquinolizine, a furocarbazole, a furophenazine, a furophenothiazine, a furophenanthridine, a furochroman an furooxolane, a furodioxine, a furoazetidine, a furoazepine, which may optionally be substituted by one or more substituents.

In one embodiment a molecule comprises for example a fully unsaturated ring structure, for example a fully saturated ring structure, for example a partly saturated ring structure, wherein such ring structure may comprise a thienopyrrole, a

thienotetrahydrofuran, a thienotetrahydropyran, a thienofuran, a thienothiophene, a thienopyrazole, an thienoimidazole, a thienofurazan, an thienooxazole, an thienoisoxazole, a thienothiazole, an thienoisothiazole, a thieno1,2,3-triazole, a thienopyridine, a thienopyridazine, a thienopyrimidine, a thienopyrazine, a thienopiperidine, a thienopiperazine, a thienomorpholine, a thienothiomorpholine, an thienoindole, an thienoisoindole, an thienoindazole, an thienoindolizine, a thienoquinoline, a thienoisoquinoline, a thienoquinazoline, a thienopteridine, a thienoquinolizine, a thienocarbazole, a thienophenazine, a thienophenothiazine, a thienophenanthridine, a thienochroman an thienooxolane, a thienodioxine, a thienoazetidine, a thienoazepine, which may optionally be substituted by one or more substituents.

In one embodiment a molecule comprises for example a fully unsaturated ring structure, for example a fully saturated ring structure, for example a partly saturated ring structure, wherein such ring structure may comprise a imidazopyrrole, a imidazotetrahydrofuran, a imidazotetrahydropyran, a imidazofuran, a imidazothiophene, a imidazopyrazole, an imidazoimidazole, a imidazofurazan, an imidazooxazole, an imidazoisoxazole, a imidazothiazole, an imidazoisothiazole, a imidazo1,2,3-triazole, a imidazopyridine, a imidazopyridazine, a imidazopyrimidine, a imidazopyrazine, a imidazopiperidine, a imidazopiperazine, a imidazomorpholine, a imidazothiomorpholine, an imidazoindole, an imidazoisoindole, an imidazoindazole, an imidazoindolizine, a imidazoquinoline, a imidazoisoquinoline, a imidazoquinazoline, a imidazopteridine, a imidazoquinolizine, a imidazocarbazole, a imidazophenazine, a imidazophenothiazine, a imidazophenanthridine, a imidazochroman an imidazooxolane, a imidazodioxine, a imidazoazetidine, a imidazoazepine, which may optionally be substituted by one or more substituents.

In one embodiment a molecule comprises for example a fully unsaturated ring structure, for example a fully saturated ring structure, for example a partly saturated ring structure, wherein such ring structure may comprise a pyrazolopyrrole, a pyrazolotetrahydrofuran, a pyrazolotetrahydropyran, a pyrazolofuran, a pyrazolothiophene, a pyrazolopyrazole, an pyrazoloimidazole, a pyrazolofurazan, an pyrazolooxazole, an pyrazoloisoxazole, a pyrazolothiazole, an pyrazoloisothiazole, a pyrazolo1,2,3-triazole, a pyrazolopyridine, a pyrazolopyridazine, a pyrazolopyrimidine, a pyrazolopyrazine, a pyrazolopiperidine, a pyrazolopiperazine, a pyrazolomorpholine, a pyrazolothiomorpholine, an pyrazoloindole, an

pyrazoloisoindole, an pyrazoloindazole, an pyrazoloindolizine, a pyrazoloquinoline, a pyrazoloisoquinoline, a pyrazoloquinazoline, a pyrazolopteridine, a pyrazoloquinolizine, a pyrazolocarbazole, a pyrazolophenazine, a pyrazolophenothiazine, a pyrazolophenanthridine, a pyrazolochroman an pyrazolooxolane, a pyrazolodioxine, a pyrazoloazetidine, a pyrazoloazepine, which may optionally be substituted by one or more substituents.

In one embodiment a molecule comprises for example a fully unsaturated ring structure, for example a fully saturated ring structure, for example a partly saturated ring structure, wherein such ring structure may comprise a oxazolopyrrole, a oxazolotetrahydrofuran, a oxazolotetrahydropyran, a oxazolofuran, a oxazolothiophene, a oxazolopyrazole, an oxazoloimidazole, a oxazolofurazan, an oxazolooxazole, an oxazoloisoxazole, a oxazolothiazole, an oxazoloisothiazole, a oxazolo1,2,3-triazole, a oxazolopyridine, a oxazolopyridazine, a oxazolopyrimidine, a oxazolopyrazine, a oxazolopiperidine, a oxazolopiperazine, a oxazolomorpholine, a oxazolothiomorpholine, an oxazoloindole, an oxazoloisoindole, an oxazoloindazole, an oxazoloindolizine, a oxazoloquinoline, a oxazoloisoquinoline, a oxazoloquinazoline, a oxazolopteridine, a oxazoloquinolizine, a oxazolocarbazole, a oxazolophenazine, a oxazolophenothiazine, a oxazolophenanthridine, a oxazolochroman an oxazolooxolane, a oxazolodioxine, a oxazoloazetidine, a oxazoloazepine, which may optionally be substituted by one or more substituents.

In one embodiment a molecule comprises for example a fully unsaturated ring structure, for example a fully saturated ring structure, for example a partly saturated ring structure, wherein such ring structure may comprise a isoxazolopyrrole, a isoxazolotetrahydrofuran, a isoxazolotetrahydropyran, a isoxazolofuran, a isoxazolothiophene, a isoxazolopyrazole, an isoxazoloimidazole, a isoxazolofurazan, an isoxazolooxazole, an isoxazoloisoxazole, a isoxazolothiazole, an isoxazoloisothiazole, a isoxazolo1,2,3-triazole, a isoxazolopyridine, a isoxazolopyridazine, a isoxazolopyrimidine, a isoxazolopyrazine, a isoxazolopiperidine, a isoxazolopiperazine, a isoxazolomorpholine, a isoxazolothiomorpholine, an isoxazoloindole, an isoxazoloisoindole, an isoxazoloindazole, an isoxazoloindolizine, a isoxazoloquinoline, a isoxazoloisoquinoline, a isoxazoloquinazoline, a isoxazolopteridine, a isoxazoloquinolizine, a isoxazolocarbazole, a isoxazolophenazine, a isoxazolophenothiazine, a isoxazolophenanthridine, a isoxazolochroman an

isoxazolooxolane, a isoxazolodioxine, a isoxazoloazetidine, a isoxazoloazepine, which may optionally be substituted by one or more substituents.

In one embodiment a molecule comprises for example a fully unsaturated ring structure, for example a fully saturated ring structure, for example a partly saturated ring structure, wherein such ring structure may comprise a thiaazolopyrrole, a thiaazolotetrahydrofuran, a thiaazolotetrahydropyran, a thiaazolofuran, a thiaazolothiophene, a thiaazolopyrazole, an thiaazoloimidazole, a thiaazolofurazan, an thiaazolooxazole, an thiaazoloisoxazole, a thiaazolothiazole, an thiaazoloisothiazole, a thiaazolo1,2,3-triazole, a thiaazolopyridine, a thiaazolopyridazine, a thiaazolopyrimidine, a thiaazolopyrazine, a thiaazolopiperidine, a thiaazolopiperazine, a thiaazolomorpholine, a thiaazolothiomorpholine, an thiaazoloindole, an thiaazoloisoindole, an thiaazoloindazole, an thiaazoloindolizine, a thiaazoloquinoline, a thiaazoloisoquinoline, a thiaazoloquinazoline, a thiaazolopteridine, a thiaazoloquinolizine, a thiaazolocarbazole, a thiaazolophenazine, a thiaazolophenothiazine, a thiaazolophenanthridine, a thiaazolochroman an thiaazolooxolane, a thiaazolodioxine, a thiaazoloazetidine, a thiaazoloazepine, which may optionally be substituted by one or more substituents.

In one embodiment a molecule comprises for example a fully unsaturated ring structure, for example a fully saturated ring structure, for example a partly saturated ring structure, wherein such ring structure may comprise a isothiaazolopyrrole, a isothiaazolotetrahydrofuran, a isothiaazolotetrahydropyran, a isothiaazolofuran, a isothiaazolothiophene, a isothiaazolopyrazole, an isothiaazoloimidazole, a isothiaazolofurazan, an isothiaazolooxazole, an isothiaazoloisoxazole, a isothiaazolothiazole, an isothiaazoloisothiazole, a isothiaazolo1,2,3-triazole, a isothiaazolopyridine, a isothiaazolopyridazine, a isothiaazolopyrimidine, a isothiaazolopyrazine, a isothiaazolopiperidine, a isothiaazolopiperazine, a isothiaazolomorpholine, a isothiaazolothiomorpholine, an isothiaazoloindole, an isothiaazoloisoindole, an isothiaazoloindazole, an isothiaazoloindolizine, a isothiaazoloquinoline, a isothiaazoloisoquinoline, a isothiaazoloquinazoline, a isothiaazolopteridine, a isothiaazoloquinolizine, a isothiaazolocarbazole, a isothiaazolophenazine, a isothiaazolophenothiazine, a isothiaazolophenanthridine, a isothiaazolochroman an isothiaazolooxolane, a isothiaazolodioxine, a

isothiaazoloazetidine, a isothiaazoloazepine, which may optionally be substituted by one or more substituents.

In one embodiment a molecule comprises for example a fully unsaturated ring structure, for example a fully saturated ring structure, for example a partly saturated ring structure, wherein such ring structure may comprise a isothiaazolopyridine, a isothiaazolopyridazine, a isothiaazolopyrimidine, a isothiaazolopyrazine, a isothiazolotriazine, a pyrimidinopyridine, a pyrimidinopyridazine, a pyrimidinopyrimidine, a pyrimidinopyrazine, a pyrimidinotriazine, a pyrazinopyridine, a pyrazinopyridazine, a pyrazinopyrimidine, a pyrazinopyrazine, a pyrazinotriazine, a pyridazinopyridine, a pyridazinopyridazine, a pyridazinopyrimidine, a pyridazinopyrazine, a pyridazinotriazine, a triazinopyridine, a triazinopyridazine, a triazinopyrimidine, a triazinopyrazine, a triazinotriazine, which may optionally be substituted by one or more substituents.

In one embodiment the molecule may comprising a lactone, a lactam, a 2-hydroxy tetrahydrofuran, a 2-alkoxy tetrahydrofuran, a 2-hydroxy tetrahydropyran, a 2-alkoxy tetrahydropyran, a benzene, a naphthalene, a phenanthrene, an anthracene, a cyclopentane, a cyclopentene, a cyclohexane, a cyclohexene, a 1,3-cyclohexadiene, a 1,4-cyclohexadiene, a cyclopentadiene, which may optionally be substituted by one or more substituents.

In one embodiment the molecule may comprising a monocyclic system, a bicyclic system, a tricyclic system, a spirocyclic system, a fused bicyclic system, wherein such cyclic systems may optionally comprise carbon atoms, silicon atoms, nitrogen atoms, phosphorous atoms, oxygen atoms, sulfur atoms, wherein such cyclic systems may optionally be substituted by one or more substituents.

In a further embodiment, two or more cyclic structures may optionally belinked by one or more bonds comprising single bonds, double bonds, triple bonds and a combination thereof, wherein such cyclic systems may optionally comprise carbon atoms, silicon atoms, nitrogen atoms, phosphorous atoms, oxygen atoms, sulfur atoms, wherein such cyclic systems may optionally be substituted by one or more substituents.

<u>Resynthesis of bifunctional complexes</u>

In some embodiments unique bifunctional complexes are resynthesized following synthesis and analysis of a library. The unique binfunctional complexes may be identified by unique codon sequences. It is then possible to mix the bifunctional complexes and then enrich certain bifunctional complexes according to e.g. affinity for a target, e.g. by performing an affinity selection. Such enriched bifunctional complexes can then be identified e.g. by quantitative PCR, hybridization or a similar method.

Also provided in the present invention is a method to obtain information on display molecules in their free form, i.e. without an identifier oligonucleotide. A display molecula can be synthesized from an initial nascent bifunctional complex with a cleavable linker. The identifier or tag of this complex may have any composition, e.g. it may be an oligonucleotide of any length or sequence, for example an oligo nucleotide of 10-40 nucleotides in length. During synthesis the nascent bifunctional complex can be purified by gel filtration (size exclusion) because the mass of the tag employed, e.g. from 3000 to 12000 dalton allows separation of the nascent bifunctional complex from reactants, buffer components and other molecular entities of small mass, which typically have masses less than 1000 dalton. Furthermore, the use of an oligonucleotide tag allows the amount of material retained during synthesis of the bifunctional complex to be estimated by measuring e.g. the optical density (OD) of the DNA by measuring absorbance at 260 nm. Alternatively, an oligonucleotide tag with an easily measurable label such as phosphor-32 or fluorescent groups is used. Following synthesis and subsequent purification of the bifunctional complex, the cleavable linker is cleaved e.g. by electromagnetic radiation, whereby the display molecule is released. The tag can then be removed from the solution containing the display molecule, e.g. by hybridizing the tag to a complementary anti-tag oligonucleotide attached to a solid phase which can easily be removed from the solution. The display molecule can then be used in any assay determining some property of the display molecule such as Ki determination versus an enzyme, Kd determination versus a protein or other target, or determination of any *in vitro* or biological parameter such as the activated partial thromboplastin time (aPTT). Removal of the tag is advantageous if the assay used to measure some property of the display molecule is sensitive to the presence of DNA. One advantage of the describe method is that the synthesis scale is on the order of nanomoles. Only a small amount of each building block (reactant) used to synthesize the bifunctional complex is therefore required. Also the building blocks (reactants) used

to synthesize the display molecule may be labelled by any method e.g. by radioactive atoms; for example the display molecule may be synthesized using on or more building blocks (reactants) containing a hydrogen-3 or carbon-14 atom. In this way a released display molecule may be used in an assay which measures some property of the display molecule by measuring the amount of label present. For example, the display molecule may be applied on one side of a layer of confluent CaCo-2 cells. Following a period of incubation the presence of label (reflecting the presence of display molecule) may be measured at each side of the confluent cell layer. Said measurements can be informative of the bioavailability of the display molecule. In another example the display molecule is applied to plasma proteins, e.g. human plasma proteins and the fraction of display molecule bound to plasma protein can be determined.

<u>Library synthesis and further processing steps</u>

When a library of different bifunctional complexes are synthesised, split-and-mix synthesis methods are employed. A plurality of nascent bifunctional complexes obtained after a first synthesis round are divided ("split") into multiple fractions. In each fraction, the nascent bifunctional complex is reacted sequentially or simultaneously with a different reactant and a corresponding oligonucleotide tag which identifies each different reactant.

The molecules (linked to their respective identifier oligonucleotides) produced in each of the fractions as disclosed herein above and in claim 1, are combined ("pooled") and then divided again into multiple fractions. Each of these fractions is then reacted with a further unique (fraction-specific) reactant and a further oligonucleotide tag identifying the reactant. The number of unique molecules present in the product library is a function of the number of different reactants used in each round of the synthesis and the number of times the pooling and dividing process is repeated.

When a library of different bifunctional complexes are synthesised, the method comprises the steps of providing in separate compartments nascent bifunctional complexes, each comprising a chemical reaction site and a priming site for enzymatic addition of a tag, and performing in any order reaction in each compartment between the chemical reaction site and one or more reactants, and

enzymatically adding the priming site one or more tags identifying the one or more reactants having participated in the synthesis of a molecule or an intermediate thereof.

The nascent bifunctional complexes in each compartment can be identical or different. In the event the nascent bifunctional complex differs at the chemical reaction site, the nascent bifunctional complex suitably comprises a tag identifying the structure of the chemical reaction site. Similar, the reactants applied in each compartment can be identical or different as the case may be. Also, the reaction conditions in each compartment can be similar or different.

Accordingly, the contents of any two or more compartments can be mixed and subsequently split into an array of compartments for a new round of reaction. Thus, in any round subsequent to the first round, the end product of a preceding round of reaction is used as the nascent bifunctional complex to obtain a library of bifunctional complexes, in which each member of the library comprises a reagent specific reaction product and respective tags which codes for the identity of each of the reactants that have participated in the formation of the reaction product.

In some embodiments, it is preferred to add the tag to the nascent bifunctional complex prior to the reaction, because it can be preferable to apply conditions for the reaction which are different form the conditions used by the enzyme. Generally, enzyme reactions are conducted in aqueous media, whereas the reaction between the reactant and the chemical reaction site for certain reactions is favoured by an organic solvent. An appropriate approach to obtain suitable condition for both reactions is to conduct the enzyme reaction in an aqueous media, lyophilize and subsequent dissolve or disperse in a media suitable of the reaction at the chemical reactive site to take place. In an alternative approach, the lyophilization step can be dispensed with as the appropriate reaction condition can be obtained by adding a solvent to the aqueous media. The solvent can be miscible with the aqueous media to produce a homogeneous reaction media or immiscible to produce a bi-phasic media.

Libraries of the present invention can be virtual libraries, in that they are collections of computational or electronic representions of molecules. The libraries may also be "wet" or physical libraries, in that they are collection of molecules that are actually

obtained through, for example, synthesis or purification, or they can be a combination of wet and virtual, with some of the molecules having been obtained and others remaining virtual, or both.

Libraries of the present invention may, for example, comprise at least about 10, at least about 50, at least about 100, at least about 500, at least about 750, at least about 1,000, or at least about 2,500 molecules or compounds.

Libraries of the present invention may also include subsets of larger libraries, i.e. enriched libraries comprising at least two members of a larger (naïve) library.

In various embodiments, at least about 40%, at least about 50%, at least about 75%, at least about 90%, or at least about 95% of the molecules of the libraries of the present invention have less than six, less than five, or, for example, less than four hydrogen bond acceptors.

In various embodiments, at least about 40%, at least about 50%, at least about 75%, at least about 90%, or at least about 95% of the molecules of the libraries of the present invention have less than six, less than five, or, for example, less than four hydrogen bond donors.

In various embodiments, at least about 40%, at least about 50%, at least about 75%, at least about 90%, or at least about 95% of the molecules or compounds of the libraries of the present invention have a calculated LogP value of less than six, less than five, or, for example, less than four.

In various embodiments, at least about 40%, at least about 50%, at least about 75%, at least about 90%, or at least about 95% of the molecules or compounds of the libraries of the present invention have a molecular weight of less than about 500, such as less than about 350, for example, less than about 300, less than about 250, or less than about 200 Daltons.

Also included in the scope of the present invention are methods and computer processor executable instructions on one or more computer readable storage devices wherein the instructions cause representation and/or manipulation, via a computer output device, of a molecule library of the present invention. Also,

methods for performing such representation and/or manipulation of a molecule library having been produced by the methods of the present invention are within the scope of the present invention.

For example, the processor executable instructions are provided on one or more computer readable storage devices wherein the instructions cause representation and/or manipulation, via a computer output device, of a library of the present invention, such as, for example, a library of scaffolded molecules, the library may comprise a plurality of molecules, wherein each molecule comprises a scaffolded part and one or more chemical entities.

The present invention also provides processor executable instructions on one or more computer readable storage devices wherein the instructions cause representation and/or manipulation, via a computer output device, of a combination of structures for analysis, wherein the combination comprises the structure of one or more members of a library of the present invention, and a biological target molecule.

In one embodiment of the invention the structure of the one or more members of the library can be represented or displayed as interacting with at least a portion of a substrate binding pocket structure of a biological target molecule. The processor executable instructions may optionally include one or more instructions directing the retrieval of data from a computer readable storage medium for the representation and/or manipulation of a structure or structures described herein.

In another aspect of the invention, combinations are provided. For example, provided in the present invention is a combination of structures for analysis, comprising a molecule library of the present invention, and a biological target molecule, wherein the structures comprise members of the library, the target molecule, and combinations thereof.

Also provided in the present invention is a combination of structures for analysis, comprising a member of a molecule library of the present invention and a biological target molecule, wherein the structures comprise the library member, the biological target molecule, and combinations thereof. The combination can be virtual, for example, computational representations, or actual or wet, for example, physical entities. In one example, at least one member of the library binds to a portion of a

ligand binding site of the target molecule. In some aspects of the combination, the concentration ratio of library members to target molecules is in a ratio of, for example about 50,000, about 25,000, about 10,000, about 1,000, about 100, or about 10 mol/mol. In some aspects of the combination, the concentration of library members is close to, at, or beyond the solubility point of the solution.

The present invention also provides a mixture for analysis by x-ray crystallography, comprising a plurality of molecules or compounds selected from a library of the present invention and a biological target molecule. The biological target molecule, may, for example, be a protein, or a nucleic acid. The biological target molecule may, for example, be crystalline.

Methods of designing novel compounds or lead candidates are also provided in the present invention. For example, in one embodiment of the present invention, a method is provided of designing a lead candidate having activity against a biological target molecule, comprising obtaining a library of the present invention, determining the structures of one or more, and in some embodiments of the invention at least two, members of the library in association with the biological target molecule, and selecting information from the structures to design at least one lead candidate.

The method can further comprise the step of determining the structure of the lead candidate in association with the biological target molecule. In one embodiment, the method further comprises the step of designing at least one second library of compounds wherein each compound of the second library comprises a scaffold and two or more chemical entities; and each compound of the second library is different. In one embodiment of the invention, the scaffold of the compounds of the second library and the scaffold of the lead candidate is the same. In one embodiment, the method further comprises the steps of obtaining the second library; and determining the structures of one or more, and in some embodiments of the invention at least two, compounds of the second library in association with the biological target molecule. The biological target molecule can be, for example, a protein or, for example, a nucleic acid. The biological target molecule may, for example, be crystalline.

The method can, for example, comprise preparing a plurality of mixtures of the biological target molecule with at least one of the molecules. The method can also,

for example, comprise preparing a mixture of the biological target molecule with a plurality of the molecules.

The method can, for example, further comprise the step of assaying the biological activity of one or more, and in some embodiments of the invention at least two, molecules against the biological target molecule. The assay may, for example, be a biochemical activity assay, or, for example, a biophysical assay, such as, for example, a binding assay, including, for example, but not limited to, an assay that comprises the use of mass spectroscopy. The biological activity assay may, for example, be conducted before, after, or simultaneously with obtaining the structure of the molecule in association with the biological target molecule.

In one example, a subset of the molecules or compounds assayed in the biological activity assay are selected for the structure determination step. In another example, a subset of the molecules or compounds used in the structure determination step are assayed in the biological activity assay. In one embodiment of the invention, the structure is determined using a method comprising X-ray crystallography. In one example, the method can further comprise the step of analyzing the binding of one or more, and in some embodiments of the invention at least two, molecules to the biological target molecule using a computational method.

In another example, the method can further comprise the steps of selecting or otherwise using information about the structures to design at least one second library, wherein the second library is derived from at least one molecule of the molecule library; and comprises compounds having modifications in at least one of the chemical entities of the scaffolded molecule. The method can, for example, further comprise the step of assaying the biological activity of one or more, and in some embodiments of the invention at least two, of the compounds against the biological target molecule.

The present invention also provides a method of designing a lead candidate having activity against a biological target molecule, comprising obtaining a library of bifunctional complexes of the present invention, determining the structures of at least one compound of the library in association with the biological target molecule, and selecting information from the structure to design at least one lead candidate.

The present invention also comprises methods where the molecule library can be screened against a first biological target molecule and eventually developed for activity against a second biological molecule. In some aspects of the invention, molecules or compounds found to have activity toward one biological target molecule can be screened against other biological target molecules where they may, for example, have the same or even enhanced activity. The second biological target molecule may, for example, be a related protein, and may, for example, be from the same protein family, for example, a protease, phosphatase, nuclear hormone receptor, or kinase family.

Thus, provided in the present invention is a method of designing a candidate compound having activity against a second biological target molecule, comprising obtaining a lead candidate of the present invention, determining the interaction of the lead candidate with a second biological target molecule; and designing at least one second library of compounds wherein each compound of the second library comprises a scaffold found in the lead candidate and modifications in at least one of the chemical entities on the scaffold.

In other methods of the invention, the molecule libraries are used in binding or biological activity assays before crystallization, and those molecules or compounds exhibiting a certain threshold of activity are selected for crystallization and structure determination. The binding or activity assay may also be performed at the same time as, or after, crystallization. Because of the ability to determine any complex structure, the threshold for determining whether a particular molecule is a hit can be set to be more inclusive than traditional high throughput screening assays, because obtaining a large number of false positives would not greatly negatively affect the process. For example, weak binders from a binding assay can be used in crystallization, and any false-positives easily weeded out. In other methods of the invention, the binding or biological activity assays can be performed after crystallization, and the information obtained, along with the structural data, used to determine the direction of the follow-up combinatorial library.

In one embodiment of the present invention, derivative compounds are selected from each library, wherein each such library comprises molecules with modifications at one chemical entity, resulting in a derived substituent, and for each library, the chemical entity that is modified is a different chemical entity, a new derivative

compound is selected having the best-scoring chemical entities in one compound. This selected derivative compound can be used as the basis of a new round of library design and screening, or can be the basis of a more traditional combinatorial library. The selected derivative compound may also be subjected to computational elaboration, in that it may serve as the basis for the individual design of an improved compound for screening. The cycle continues until a new derivative compound is obtained that can be considered to be a lead compound, having a desired IC_{50}, and other desirable lead compound properties.

The present invention also provides methods for designing the molecule and compound libraries of the present invention. Provided in the present invention is a method of designing a molecule library for drug discovery, comprising screening or reviewing a list of synthetically accessible or commercially available molecules, and selecting molecules for the library wherein each of the molecules comprises: two or more chemical entities and preferably less than 25 non-hydrogen atoms. The molecules of the library may, for example, comprise, in their scaffold, at least one single or fused ring system. The molecules of the library may, for example, comprise in their scaffold at least one hetero atom on at least one ring system.

Also provided in the present invention is a method of screening for a molecule for use as a base molecule for library design, comprising obtaining a library of the present invention, screening the library for members having binding activity against a biological target molecule; and selecting a molecule of member(s) with binding activity to use as a base molecule for library design.

Also provided in the present invention are lead candidates and candidate compounds obtained by the methods of the present invention, libraries obtained by the methods of the present invention, and libraries comprising compounds with molecules selected by the methods of the present invention.

The present invention also provides a method of designing a lead candidate having biophysical or biochemical activity against a biological target molecule, comprising obtaining the structure of the biological target molecule bound to a molecule, wherein the molecule comprises a substituent having anomalous dispersion properties, synthesizing a lead candidate molecule comprising the step of replacing a chemical entity or derived substituent on the compound with a substituent

comprising a functionalized carbon, nitrogen, oxygen, sulfur, or phosphorus atom, and assaying the lead candidate molecule for biophysical or biochemical activity against the biological target molecule.

The present invention also provides a method of designing a lead candidate having biophysical or biochemical activity against a biological target molecule, comprising combining a biological target molecule with a mixture comprising one or more, and in some embodiments of the invention at least two, molecules or compounds, wherein at least one of the molecules or compounds comprises a substituent having anomalous dispersion properties, identifying a molecule bound to the biological target molecule using the anomalous dispersion properties of the substituent, synthesizing a lead candidate molecule comprising the step of replacing the anomalous dispersion substituent with a substituent comprising a functionalized carbon or nitrogen atom, and assaying the lead candidate molecule for biophysical or biochemical activity against the biological target molecule.

Design of libraries

A vast number of different libraries may be designed that can be synthesized by methods of the present invention. The library may be designed using a number of approaches known to a person skilled in the art. Library design (i.e. the choice of reactants, linker, and tags which shall be used for the synthesis of a library) may consist of a number of steps including but not limited to:

I. Choosing the linker type, e.g., the linker may be chosen to have a single chemical reaction site, two chemical reaction sites or more. The chemical reaction site may be chosen to be an amine, an acid, an aldehyde or a C-X group where X is a halogen.
II. Choosing the number of reactants to be used at each cycle during library synthesis
III. Choosing the type of reactants such as
    a. reactants with a single reactive group such as a –COOH group, an amine, an isocyanate, a sulfonyl halogen, an aldehyde or a C-X group where X is a halogen, and/or
    b. reactants with two reactive groups chosen from the group of a –COOH group, an amine, an isocyanate, a sulfonyl halogen, an aldehyde or a C-X group where X is a halogen, and/or

c. reactants with three reactive groups chosen from the group of a –COOH group, an amine, an isocyanate, a sulfonyl halogen, an aldehyde or a C-X group where X is a halogen.
d. reactants with four reactive groups chosen from the group of a –COOH group, an amine, an isocyanate, a sulfonyl halogen, an aldehyde or a C-X group where X is a halogen.
e. reactants with five reactive groups chosen from the group of a –COOH group, an amine, an isocyanate, a sulfonyl halogen, an aldehyde or a C-X group where X is a halogen.
f. reactants with six reactive groups chosen from the group of a –COOH group, an amine, an isocyanate, a sulfonyl halogen, an aldehyde or a C-X group where X is a halogen.
g. All or some of the reactive group may be appropriately protected using a protection group known to a person skilled in the art such as an fmoc group, a nosyl group, an msec group, a boc group or a tBu group (see general procedures for details).

IV. Choosing the number of each type of reactants to be used at each cycle during library synthesis.

V. Analyzing reactants with regards to properties such as molecular weight, octanol/water and water/gas log Ps, log S, log BB, overall CNS activity, Caco-2 and MDCK cell permeabilities, human oral absorption, log Khsa for human serum albumin binding, and log IC50 for HERG K+-channel blockage logD, number of hydrogen bond donors or acceptors, rotational bonds, polar surface area, Lipinski Rule-of-Five violations, drug-likeness or lead-likeness etc. Said properties may be predicted e.g. using a computer program such as qikprop (www.schrodinger.com) or determined in an assay by a person skilled in the art.

VI. Comparing reactants with other reagents with regards to structural of functional similarity

VII. Enumerating the library to be synthesized, i.e., virtually (e.g. using a computer) constructing all possible encoded molecules.
a. Analyzing said molecules with regards to properties such as molecular weight, octanol/water and water/gas log Ps, log S, log BB, overall CNS activity, Caco-2 and MDCK cell permeabilities, human oral absorption, log Khsa for human serum albumin binding, and log IC50 for HERG K+-channel blockage logD, number of hydrogen bond

donors or acceptors, rotational bonds, polar surface area, Lipinski Rule-of-Five violations, drug-likeness or lead-likeness etc. Said properties may be predicted e.g. using a computer program such as qikprop (www.schrodinger.com) or determined in an assay by a person skilled in the art.

b. Comparing said molecules with other molecules with regards to structural of functional similarity

VIII. Testing the reaction efficiency of reactants before using them for library synthesis.

IX. Generating one or more encoded molecules using reactants from an initial list of reactants to be used for the synthesis of a specific library, subjecting said encoded molecule(s) to one or more assays, and adjusting said list of reactants (i.e. removing reactants from the list or adding reactants to the list) based on the results of said assays.

X. Choosing reactants based on prior information regarding a target or a related molecule on which a library is intended to be screened. The related molecule may be one or more parts of a target, a molecule derived from a target e.g. by mutation, a molecule which is related to the target e.g. another member of the target family, a target homolog etc. Said prior information may be

a. structural information obtained by x-ray crystallography or NMR or another method

b. structural information obtained by x-ray crystallography or NMR or another method in the presence of ligand and/or cofactor

c. structural information obtained by x-ray crystallography or NMR or another method in the presence of a molecule or fragment such as a reactant or a reactant analog

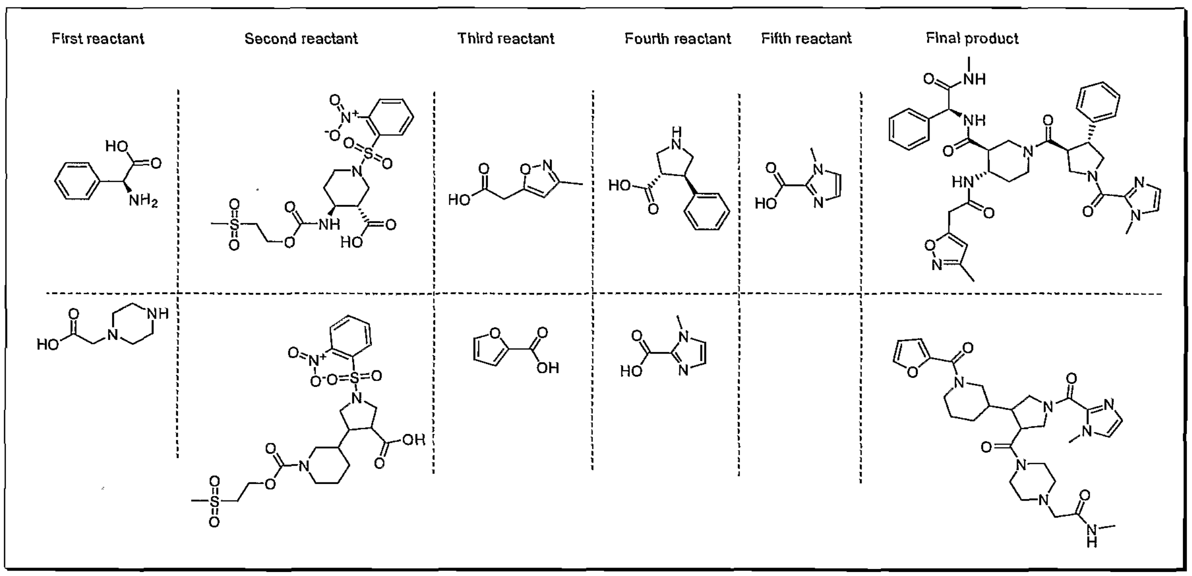
d. information obtained by mutagenesis followed by an assay which can be performed by a person skilled in the art.

e. structure-activity information obtained e.g. by synthesis of a series of molecules followed by testing of the molecules in an appropriate assay. Such information may suggest reactants which are identical or similar to parts of said tested molecules.

XI. Choosing reactants based on prior information obtained by synthesis of a library followed by screening of the library and analyses of the screening results. Said library being synthesized by the methods described by the current invention or related methods for synthesizing bifunctional molecules

such but not limited to those described in Rasmussen (2006) WO 06/053571A2, Liu et al. (2002), WO 02/074929 A2; Pedersen et al. (2002) WO 02/103008 A2; Pedersen et al. (2003) WO03/078625 A2; Harbury and Halpin, WO 00/23458, and Hansen et al WO 06/048025.

In some embodiments it is preferred that each display molecule has the same general structure. In other embodiments it is preferred that display molecules may have different general structures, e.g. be composed from a different number of chemical entities:



This can be achieved e.g. by subjecting to library to a final reactant reaction step. The reactant can only react with display molecules that have a corresponding reactive group. Thus, the finalized library may contain display molecules of different general structures, e.g., be composed of a different number of entities.

Preferred split-and-mix methods

In preferred embodiments there are provided methods for preparing a large combinatorial library of compounds which has the advantages of (i) massive parallel synthesis of subunits and known, addressable library positions, (ii) adaptable to virtually any oligomer or small-molecule chemistry, (iii) a relatively large area for synthesis of each library member, (iv) capable of being screened either as a mixture or as individual library compounds in either solution phase or solid phase, and (v)

capable of amplifying and modifying selected library compounds.

The principle advantage of the below-disclosed embodiments is that the tag directs and encodes the synthesis of the compound to which it is covalently attached (not merely reporting on the synthetic history of individual compounds), the tag can be used to create library subpopulations based on hybridization, the types of compounds that are synthesized are not limited to polypeptides and polynucleotides, the number of compounds that can be produced far exceeds that of traditional combinatorial libraries and the tag comprises or consists of a nucleic acid molecule which can be amplified biochemically and improved by genetic recombination, and in vitro evolution. The nucleic acid molecule can comprise any of the nucleotides disclosed herein above.

In one aspect of the present invention, the below disclosed split-n-mix methods are carried out subsequently to the above-disclosed methods for obtaining a bifunctional complex comprising a molecule and an identifier oligonucleotide, wherein, initially, a nascent bifunctional complex comprising one or more chemical reaction site(s) and one or more priming site(s) for enzymatic addition of a tag is reacted, in any order, a) at the chemical reaction site with one or more reactant(s) in the form of reactants or chemical entities and b) reacted at the priming site with one or more identifier oligonucleotide tag(s) identifying the reactant(s) which have reacted - or are going to react - with each other and/or with the chemical reaction site, wherein tag ligation results in the formation only of a single stranded identifier oligonucleotide comprising a plurality of tags, whereas no anti-tag at least partly hybridised the one or more tags are ligated to a neighbouring anti-tag. Subsequently to this method, the below disclosed embodiments are carried out, optionally after having selected desirable bifunctional complexes from the first synthesis method, and further optionally after having amplified the identifier oligonucleotide of one or more of said selected bifunctional complexes. The amplification can be carried out when the identifier oligonucleotide is attached to the molecule of the bifunctional complex, or the amplification can occur after the identifier oligonucleotide has been released from the remaining part of the bifunctional complex.

Accordingly, in one embodiment there is provided further method steps and compositions for further iterative synthesis and further screening of a plurality of compounds wherein a nucleic acid tag directs and encodes the synthesis of the

compound to which it is covalently attached, and the tag is a DNA molecule which can be amplified biochemically.

The further methods of the present invention provide for synthesis of a plurality of compounds in a combinatorial library by way of a split and combine synthesis strategy, wherein synthesis is directed by the nucleic acid tag. The library can be provided in solution or attached to a solid support.

The nucleic acid tags useful in the methods of the present invention comprise nucleic acid sequences having a plurality of different first hybridization sequences, a mixture of different second hybridization sequences, and a chemical reaction site.

The present invention further provides a library of nucleic acid tags, also termed nucleic acid supports for use in directing the synthesis of a plurality of compounds wherein each tag has a first segment having a selected one of a plurality of different first hybridization sequences, a mixture of different second hybridization sequences, and a chemical reaction site; and a second segment having a selected one of a plurality of different second hybridization sequences and a mixture of different first hybridization sequences.

The further methods of the present invention provide subsets of nucleic acid tags generated by base-specific duplex formation between each different first or second hybridization sequence and a complementary oligonucleotides or oligonucleotide analogs. The chemical reaction sites in each of the subsets are reacted with a selected reagent to form a reagent-specific compound intermediate.

The further methods of the present invention also provide that the steps of formation of subsets of nucleic acid sequences by base-specific duplex formation be repeated and a chemical subunit added to the chemical reaction site or last added chemical subunit within each subset until synthesis of the plurality of compounds is complete.

In an exemplary aspect of the present invention, the nucleic acid tags include alternating spacer and hybridization sequences, wherein the spacer sequences are the same for all subsets of nucleic acid sequences and the hybridization sequences are different for each subset of nucleic acid sequences.

In a related aspect, the spacer sequence portion of each nucleic acid sequence has a restriction enzyme site which is unique to a given spacer sequence.

The methods of the present invention provide for the synthesis of small molecules with different chemical sequences, catalysts useful for the synthesis of complex molecules from simple substrates, inorganic compounds with useful properties as materials, non-ribosomally produced polypeptides, peptoids, polyketide-based natural products or subunit oligomers, e. g., polypeptides, polynucleotides etc. as disclosed herein above.

In one embodiment, the invention provides compound libraries wherein the compounds of such libraries can be subjected to enrichment for one or more desired activities on a continuously amplifying population.

In the methods of the present invention compounds having one or more desired activities are enriched to yield a subpopulation of nucleic acid sequences. The enriched subpopulation (s) of nucleic acid sequences serve as the starting material for repeating the step-wise synthesis of additional compounds.

Alternatively, the enriched subpopulation of nucleic acid sequences is amplified by nonspecific polymerase chain reaction (PCR), and a new chemical reaction site added prior to repeating the step-wise synthesis of additional compounds.

A process termed "polynucleotide or gene shuffling" may also be applied to the present invention. In such a process, the enriched subpopulation of nucleic acid sequences is treated with one or more restriction enzymes under conditions effective to produce a partial digest by cleavage at a sequence-specific restriction enzyme site within each spacer sequence. The partially digested nucleic acid sequences are rejoined and a new chemical reaction site added prior to repeating the step-wise synthesis of additional compounds.

Compound libraries which are synthesized under the direction of compound-specific synthesis-directing nucleic acid tags are also provided by the present invention. In this aspect, the nucleic acid sequences which direct the synthesis of the compounds can be subjected to genetic recombination or in vitro evolution by repeated cycles of enrichment and step-wise synthesis; enrichment, PCR amplification and step-wise

synthesis; or enrichment, partial digestion, rejoining of fragments and stepwise synthesis to yield a highly enriched subpopulation of synthesis-directing nucleic acid sequences.

Preferably, subpopulations of enriched compounds are produced by the methods of the present invention by selecting for activities which include, but are not limited to, modulation of enzymatic activity, modulation of non-enzymatic catalytic activity, modulation of protein-protein interactions and modulation of receptor/ligand interactions, etc.

The invention also provides a method for library splitting on the basis of sequence hybridization post-synthesis. In this aspect, a complete library is synthesized, split by hybridization based on the different sequence directing nucleic acid tag attached to each library member and further step performed on the split library.

The invention also provides a method for library splitting on the basis of sequence hybridization following enrichment of certain bifunctional complexes, e.g. by affinity selection. In this aspect, a complete library is synthesized, subjected to affinity selection and split by hybridization based on the different sequence directing nucleic acid tag attached to each library member. Then further steps may be performed on the split library such as decoding tags of individual split library pools by sequencing.

Preferred types of compounds in the compound libraries of the present invention include, but are not limited to, small molecules with different chemical sequences, catalysts useful for the synthesis of complex molecules from simple substrates, inorganic compounds with useful properties as materials, non-ribosomally produced polypeptides, peptoids, polyketide-based natural products or subunit oligomers, e. g., polypeptides, polynucleotides etc.

Further, the invention provides a method to perform all genetic manipulations possible with natural biopolymers (through the manipulation of DNA instructions) on such DNAtemplated combinatorial libraries of compounds as a means to provide a method to identify useful compounds from large combinatorial libraries of compounds, as described above.

These and other objects and features of the invention will become more fully

apparent when the following detailed description of the invention is read in conjunction with the accompanying drawings.

Definitions

The term"combinatorial library"is defined herein to mean a library of molecules containing a large number, typically between 10e3 and at least 10e6, such as 10e8, for example 10e10 different compounds typically characterized by different sequences of subunits, or a combination of different sequences of side chains and linkages.

The term"combinatorial library of subunit oligomers"is defined herein to mean a set of oligomers containing substantially each sequence permutation that can be formed by placing a selected one of a number of different subunits at each of a selected number of residue positions.

"Different-sequence oligomer compounds"are oligomers, such as oligonucleotides, oligonucleotide analogs, oligopeptides, oligopeptide analogs, oligosaccharides, or lipopeptides with different permutations of lipid and/or sequences in the peptide moieties, glycopeptides with different sequence permutations in the saccharide and/or peptide moieties, non-biological oligomers with different-sequence permutations, or different-substituent compounds in a small molecule library.

The terms "base-specific duplex formation" or "specific hybridization"refer to temperature, ionic strength and/or solvent conditions effective to produce sequence-specific pairing between a single-stranded oligonucleotide and its complementary-sequence nucleic acid strand, for a given length oligonucleotide. Such conditions are preferably stringent enough to prevent or largely prevent hybridization of two nearly-complementary strands that have one or more internal base mismatches. Preferably the region of identity between two sequence s forming a base-specific duplex is greater than about 5 bp, more preferably the region of identity is greater than 10 bp.

The terms "polymerase chain reaction" and "PCR" refer to a process of amplifying one or more specific nucleic acid sequences, wherein (i) oligonucleotide primers which determine the ends of the sequences to be amplified are annealed to single-stranded nucleic acids in a test sample, (ii) a nucleic acid polymerase extends the

3'ends of the annealed primers to create a nucleic acid strand complementary in sequence to the nucleic acid to which the primers were annealed, (iii) the resulting double-stranded nucleic acid is denatured to yield two single-stranded nucleic acids, and (iv) the processes of primer annealing, primer extension, and product denaturation are repeated enough times to generate easily identified and measured amounts of the sequences defined by the primers. The sequential annealing, extension and denaturation steps are controlled by varying the temperature of the reaction container, normally in a repeating cyclical manner. Annealing and extension are typically carried out between 40-80 C, whereas denaturation requires temperatures between about 80 and 100 C. A "thermal cycler", such as Perkin Elmer Model 9600, is typically used to regulate the reactions.

The terms "oligonucleotides" or "oligos" as used herein refer to nucleic acid oligomers containing between about 3 and typically up to about 150, such as from about 5 to about 100 nucleic acid subunits, for example from about 5 to about 80 nucleic acid subunits. In the context of oligos which direct the synthesis of the library compounds of the present invention, the oligos may include or be composed primarily of nucleotide analog subunits, or other subunits capable of forming sequence-specific Watson-Crick base pairing, when assembled in a linear polymer, with the proviso that the free ends of the oligos are ribonucleotide or deoxyribonucleotide subunits capable of providing a suitable substrate for strand-directed polymerization in the presence of a DNA polymerase and one or more nucleotide triphosphates, e. g., conventional deoxyribonucleotides with free 3'OH groups. A"knownsequence oligo"is an oligo whose nucleic acid sequence is known.

The term"oligonucleotide analog"is defined herein to mean a nucleic acid that has been modified and which is capable of some or all of the chemical or biological activities of the oligonucleotide from which it was derived. An oligonucleotide analog will generally contain phosphodiester bonds, although in some cases, oligonucleotide analogs are included that may have alternate backbones. (See, E. G., several nucleic acid analogs described in Rawls, C & E News, June 2,1997, page 35). Modifications of the ribose-phosphate backbone may facilitate the addition of additional moieties such as labels, or can be done to increase the stability and half-life of such molecules. In addition, mixtures of naturally occurring nucleic acids and analogs can be made. Alternatively, mixtures of different nucleic acid analogs, and mixtures of naturally occurring nucleic acids and analogs can be made. The

oligonucleotides can be single stranded or double stranded, as specified, or contain portions of both double stranded or single stranded sequence. The oligonucleotide can be DNA, RNA or a hybrid, where the nucleic acid contains any combination of deoxyribo-and ribo-nucleotides, and any combination of bases, including uracil, adenine, thymine, cytosine, guanine, inosine, xathanine hypoxathanine, isocytosine, isoguanine, etc.

The"subunit oligomers"produced by the methods of the present invention typically have 3 to 20 residue positions at which the subunit assumes one of a plurality of possible forms, e. g., different nucleic acid or amino acid side chains.

"Different-sequence small-molecule compounds"are small organic molecules, typically, but not necessarily, having a common parent structure, such as a ring structure, and a plurality of different R group substituents or ring-structure modifications, each of which takes a variety of forms, e. g., different R groups. Such compounds are usually non-oligomeric (that is, do not consist of sequences of repeating similar subunits) and can be similar in terms of basic structure and functional groups, but vary in such aspects as chain length, ring size or number, or patterns of substitution.

The term"chemical reaction site"as used herein refers to a chemical component capable of forming a variety of chemical bonds including, but not limited to; amide, ester, urea, urethane, carbon-carbonyl bonds, carbon-nitrogen bonds, carbon-carbon single bonds, olefin bonds, thioether bonds, and disulfide bonds.

The terms"nucleic acid tag"and"nucleic acid support"are defined herein to mean the nucleic acid sequences which comprise a plurality of different first hybridization sequences, a mixture of different second hybridization sequences, and a chemical reaction site. Such"nucleic acid tags"are capable of directing the synthesis of the combinatorial library of the present invention and a re also termed"synthesis-directing nucleic acid tags".

The term"tag-directed synthesis"refers to the fact that the plurality of compounds synthesized by the methods of the present invention is directed by the nucleic acid tag.

The term"continuously amplifying population"refers to the continuously increasing plurality of compounds produced by the iterative methods of the present invention.

The term"genetic recombination"refers to enrichment of the plurality of compounds produced by the methods of the present invention for those compounds having one or more desired activities by performing the steps of enrichment, partial digestion, rejoining the partially digested sequences and further stepwise synthesis to yield a highly enriched subpopulation of nucleic acid sequences which are bound to compounds having one or more desired activities.

The term “nucleic acid tag(s)” are used interchangably herein below with identifier oligonucleotide(s) comprising a plurality of nucleic acid tags.

In another aspect, the invention provides combinatorial compound libraries which can be subjected to genetic recombination or in vitro evolution by repeated cycles of enrichment and step-wise synthesis, enrichment, PCR amplification and step-wise synthesis or enrichment, partial digestion, reformation and stepwise synthesis to yield a highly enriched subpopulation of nucleic acids which are bound to compounds having one or more desired activities.

The term"selection for a desired activity"means evaluating one or more of the plurality of compounds produced by the methods of the invention for the ability to modulate a chemical or biological reaction.

The term"receptor"refers to a molecule that has an affinity for a given ligand which can be naturally occurring or synthetic molecule. Receptors can be attached, covalently or noncovalently, to a binding member, either directly or via a specific binding substance. Examples of receptors include, but are not limited to, antibodies, including monoclonal antibodies and antisera reactive with specific antigenic determinants (such as on viruses, cells, or other materials), cell membrane receptors, complex carbohydrates and glycoproteins, enzymes, and hormone receptors.

The term"ligand"refers to a molecule, such as a random peptide or variable segment sequence, that is recognized by a particular receptor. As one of skill in the art will recognize, a molecule (or macromolecular complex) can be both a receptor and a

ligand. In general, the binding partner having a smaller molecular weight is referred to as the ligand and the binding partner having a greater molecular weight is referred to as a receptor.

The term"modulate"as used herein refers to a change in a particular biological activity.

Modulation may relate to an increase or a decrease in biological activity, binding characteristics, or any other biological, functional, or immunological property of the molecule.

The term"agonist"as used herein, refers to a molecule which is capable of modulating a biological activity of, e. g., a receptor by inducing, increasing, or prolonging the duration of the biological activity mediated by the receptor. Agonists may themselves be polypeptides, nucleic acids, carbohydrates, lipids, or derivatives thereof, or any other molecules which bind to and modulate the activity of the receptor.

The term"antagonist"as used herein, refers to a molecule which, when bound to, e. g., a receptor modulates the activity of the receptor by blocking, decreasing, or shortening the duration of the biological activity mediated by the receptor. Antagonists may themselves be polypeptides, nucleic acids, carbohydrates, lipids, or derivatives thereof, or any other molecules which bind to and modulate the activity of the receptor.

Other terms used herein should be construed to take on meanings customary in the art, unless otherwise defined herein.

Templated resynthesis of libraries of bifunctional molecules

Methods disclosed herein allows for the synthesis of libraries of bifunctional molecules and for the subsequent partitioning such as affinity selection of libraries for the purpose of the identification of library molecules with a desired function.

In some cases it may be beneficial that the identifier tag information that is amplified following the partioning step can be used to direct the re-synthesis of the first library for subsequent further partitioning and identification of desired molecules.

Consequently, following an initial split-and-mix synthesis of a library of bifunctional molecules according to the present invention and as disclosed herein and a subsequent partitioning step and optionally amplification of the identifier tags (identifier oligonucleotides) of selected molecules, the tags or tag amplification product(s) can be used as a template for the re-synthesis of the first library or a subset of the first library using any process that allows the information of the amplified identifier to direct a templated synthesis of the library.

Following templated synthesis, the generated second library can be partitioned and the template amplified for identification of desired molecules by e.g. sequencing of the isolated identifiers (templates). Alternatively the amplified template can be used to template the synthesis of a third library being identical to or a subset of the first or the second library using any process that allows the templated synthesis of a library of bifunctional molecules. The process of library resynthesis, partitioning and template amplification can be iterated any number of times such as 1 time, 2 times, 3 times, 4 times, 5 times, 6 times, 7 times, 8 times, 9 times, 10 times or more than 10 times.

Methods that can be used for templated library resynthesis includes but is not limited to (Rasmussen (2006) WO 06/053571A2, Liu et al. (2002), WO 02/074929 A2; Pedersen et al. (2002) WO 02/103008 A2; Pedersen et al. (2003) WO03/078625 A2; Harbury and Halpin, WO 00/23458, Hansen et al WO 06/048025. In the method disclosed by Harbury and Halpin, free reactants are loaded on the reactive site on the identifier in solution or attached to a solid-support. This method of reactant loading in free form is similar to the methods disclosed herein. Consequently, the building block reactants applied for a first library of bifunctional molecules is directly applicaple to the templated process described by Halpin and Harbury for second library synthesis. Other methods for templated synthesis listed above (Rasmussen (2006) WO 06/053571A2, Liu et al. (2002), WO 02/074929 A2; Pedersen et al. (2002) WO 02/103008 A2; Pedersen et al. (2003) WO03/078625 A2; Hansen et al WO 06/048025 A1, requires the pre-attachment of reactants to oligonucleotides prior to the chemical reactions required for the templated synthesis of a second library. Thus, none of the building block reactants applied in a first library synthesis using the method disclosed herein is directly applicable to the synthesis of a second library without prior modification of the reactants and/or appendage to an oligonucleotide.

The following example is included to illustrate the principle of templated resynthesis of a library using templates that are amplified from a pool of identifiers isolated from the screening of a first library of bifunctional molecules.

Synthesis of a first library is conducted as described elsewhere in the claims and in example 1 producing a library consisting of app 65.000 different bifunctional molecules. The tetramer library consists of bifunctional molecules each comprising 4 DNA codon elements (tags) covalently linked to the cognate chemical fragments. The overall structure of the bifunctional molecules is shown in figure 51. Each 20 nt/bp codon is spaced by a 10 nt fixed region and the tags A-D is flanked by fixed sequences useful for amplification by PCR.

The 65.000 member library was screened against thrombin and the isolated DNA was amplified as described in example 1 using proof-reading PCR and the forward and reverse primers 5'-CAAGTCACCAAGAATTCATG and 5'-AAGGAACATCATCATGGAT. The PCR product was used as template for large-scale 96 wells proof-reading PCR (Pwo Master- mix, Roche) using a similar primer pair except that the forward primer contained the NH_2-PEG unit described in example 1 and the reverse primer contained a 5'-biotin group. Following PCR, the content of all wells was pooled, extracted twice with phenol and once with chloroform before ethanol/acetate precipitation of the DNA. Following centrifugation the DNA pellet was washed twice using 70%ethanol, dried and redissolved in 100 ul of 25 mM NH_4-acetate pH 7.25. 100 ul SA-beads (Amersham) is washed 3 times with 25 mM NH_4-acetate buffer before mixing with the DNA sample and incubation for 10 min at RT. The sample is washed 3 times with ammonium-acetate buffer. The non-biotinylated topstrand comprising the 5' Amino-PEG unit was eluted by adding 200 ul of H_2O at 90 °C for 30 seconds before immediate spin removal of the SA-beads using a SpinX column (Corning). The singlestranded template is incubated with another 100 ul of SA-beads and incubated for 10 min at RT before SA-bead removal using SpinX column. The unbound fraction is purified on a microspin 6 column (Bio-rad). This sample containing a singlestranded template with terminal Amino-PEG unit was used for the templated resynthesis of the second library essentially according to the method of Halpin and Harbury: DNA Display I. Sequence-Encoded Routing of DNA Populations,
PLoS Biol. 2004 July; 2(7): e173. DNA Display II. Genetic Manipulation of Combinatorial Chemistry Libraries for Small-Molecule Evolution, *PLoS Biol.* 2004

July; 2(7): e174. DNA Display III. Solid-Phase Organic Synthesis on Unprotected DNA, *PloS Biol.* 2004 July 2(7): e175.

In brief, the singlestranded template is allocated according to the codon sequence in position A into specific compartments by hybridization to a complementary anti-tag immobilised to a solid-support. Consequently, 16 different anti-tags each capable of hybridizing specifically to one A-codon tag is immobilised on solid-support, placed in individual housings and connected in series. The template is pumped through the compartments in a circular system until the templates are allocated in their cognate compartments. Subsequently, each template is transferred to a DEAE column for chemical reaction with a codon specific building block (reactant) according to Table 1.4A. Following chemical transformation and deprotection, all templates are collected from the DEAE column, pooled and redistributed into specific codon B compartments in a process similar to that described above for position A. Consequently the allocation, chemical reaction, deprotection, pooling steps can be iterated for codon positions A to D ultimately producing a library a bifunctional molecules using the same building block/codon combinations as for the initial library enabling the resynthesis of this library based on the identifier/template bias created from the partitioning of the first library.

<u>Templated synthesis of a library of bifunctional complexes using identifier allocation by sequential identifier subtraction.</u>

Several methods have been disclosed for the templated synthesis of a library of bifunctional molecules such as (Rasmussen (2006) WO 06/053571A2, Liu et al. (2002), WO 02/074929 A2; Pedersen et al. (2002) WO 02/103008 A2; Pedersen et al. (2003) WO03/078625 A2; Harbury and Halpin, WO 00/23458, Hansen *et al* WO 06/048025. All methods except for DNA-display (Harbury and Halpin) employ the pre-attachment of reactants to specific oligonucleotide sequences capable of hybridising to a specific codon on the template. This pre-attachment is time- and resource consuming and limits the number of commercially available reactants for library generation. In contrast, the chemical transformation using free-form reactants (Halpin and Harbury) dramatically increase building block access, number of chemical reactions available for library generation and reduce time and resources necessary for preparation of reactants. Consequently, the free-form reactant offers a clear advantage for the fast access to and diversity of chemical transformations.

However, the method disclosed by Halpin and Harbury requires specific allocation of the identifier templates into discrete compartments. This allocation is conducted by passing the pool of identifier templates through a series of compartments comprising compartment specific anti-tags oligonucleotides attached to a solid-support. Such compartment specific allocation is difficult due to problems with unspecific template allocation resulting in a template being fortuitously trapped in compartments with a non-cognate anti-tag. Ultimately, this results in an illegal reactant/codon combination and a reduced fidelity in translation of the template. Furthermore, the single stranded form of DNA is energetically disfavoured and a complex ssDNA template will tend to take up secondary structure which may result in template loss during an allocation step due to lack of hybridisation to a cognate anti-tag. Also, the hybridisation between two complementary oligonucleotide sequences may be impeded to some extent by the covalent attachment of one oligonucleotide component (anti-tag) to a solid-support compared to a similar duplex formation performed in solution.

The issues above could be resolved by performing the hybridization between a specific anti-tag or a subset pool of anti-tags and the complementary identifier sequence(s) in solution. This allows the experimenter to remove secondary structures in the template f. ex by a heat denaturation step prior to anti-tag hybridization for improved hybridization kinetics. Subsequently, the anti-tag/identifier duplexes needs to be retracted from the remaining unbound fraction of identifiers in a first allocation step using a handle supplied on the anti-tag such as a biotin-group for specific isolation using SA(streptavidin)-beads. Following retraction of the first subset of identifiers the remaining pool of unbound identifiers is denatured before addition of the next specific anti-tag or subset of anti-tags and the process of identifier subset isolation is iterated until all identifiers are allocated on their sequence specific subset SA-beads.
Obviously, an iterative process involving fishing out single specific codon identifier sequences may become unfeasible for large codon sets. Consequently, the entire pool of individual (single) anti-tag sequences complementary to the pool of codons at one position such as position A in the template shown in the figure below, can be subdivided into a subset pool of anti-tags. The subset pools can then be used for sequential subtraction of identifier templates into discrete pools. Following elution of identifiers from each retracted sub-pool the single-stranded identifiers are hybridised to a smaller subset of anti-tags than used for initial round of allocation or using a

single anti-tag from the corresponding first round subset. The sequential subtraction can be iterated until each identifier is allocated in separate compartments according to its unique first codon sequence.

The example below (see figure 52) is included to illustrate the use of sequential subtraction. Initially, 10 subset pools ***a- j*** each comprising 10 anti-tag totalling 100 anti-tag sequences for codon position A is prepared carrying a purification handle (f. ex a biotin-group).

i) A singlestranded identifier with a reactive entity is provided.

ii) 1st capture: combine anti-tags complementary to codon position A in different 10 different pools (***a-j***) each having 10 anti-tags:
(***a***)1-10, (***b***)11-20, (***c***)21-30, (***d***)31-40, (***e***)41-50, (***f***)51-60, (***g***)61-70, (***h***)71-80, (***i***)81-90, (***j***)91-100.

iii) Add pool ***a*** to identifier and hybridize anti-tags to the cognate subset of identifiers in solution or on solid support. The bound fraction is subtracted from the pool using the anti-tag handle.

iv) The fraction of unbound identifiers is hybridized to pool ***b*** and subtracted from the identifier pool as above

v) Continue the identifier subset subtraction using anti-tag pool ***a*** to ***j***.

vi) Elute single-stranded identifier into pool ***a*** to ***j***

vii) 2nd capture: The subset capture method described above is used for each subset a to j applying single anti-tags.Consequently, from pool a, anti-tag 1 is used as a first hybridizing anti-tag allowing specific subtraction of identifiers with a codon 1 at position A. The unbound pool of identifiers is subsequently hybridized with anti-tag 2 for specific subtraction of identifiers with codon 2 at position A.

viii) Repeat identifier subset allocation using all 10 single anti-tag within specific subgroup allowing specific (single) allocation of identifiers in 100 subset groups.

ix) Chemical reaction using specific reactant/codon combinations and subsequent deprotection

x) Pool identifiers and repeat routing principle for codon position B

In the example above, two branch allocations are conducted for each specific

identifier (ie each codon sequence is subset allocated twice). In the first round each identifier is allocated as a subset pool followed by a second specific allocation for each unique codon. However, the experimenter may choose any number of branches, any number of subset pools at each branch and any number of anti-tags in each subset pool. Furthermore, the specific routing conducted for one position is custom-made for that codon position and, consequently, the experimenter can re-use the branch-profile from one position to any of the remaining positions or may apply a branch profile that is unique for a codon position.
Also, the experimenter may use any number of branches such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more than 10 branches in the routing protocol. Furthermore, the experimenter can use any number of subset pools such as any number between 1 and 1.000 or more than 1.000. Also the experimenter can use any number of anti-tags in each subset pool such as any number between 1 and 1.000 or more than 1.000.

The use of multiple branches increase the specificity of the allocation step, because the level of unspecific allocation is reduced when conducting more than a single allocation round as described Halpin and Harbury WO 00/23458. In the example below, a principle for sub-allocation of 200 different codons at position for a pool of identifier templates is described using 3 branches. In the first branch 5 pools of anti-tags each comprising 40 unique anti-tags is used for the sequential subtraction of identifiers into their cognate sub-pools. Following elution of identifiers in each sub-pool, the second branch of allocation is conducted using a subset of 5 pools of 8 anti-tags each, for the specific retrieval of subsets within their respective 1st branch subset producing a total of 25 sub-pools. Following identifier elution, the 3rd branch of subset allocation is conducted using each unique anti-tag individually for identifier retrieval subtracted from their cognate subset pool from the 2nd branch resulting in specific single allocation of identifiers containing a unique codon at position A. Subsequently, the identifiers can be eluted e.g. in H2O as described herein elsewhere and prepared for chemical transformation using a codon-specific reactant, reacted, optionally purified, optionally deprotected and pooled before re-allocation according to the next codon position of the identifier template. The process is iterated any number of times dependent on the number of chemical reactant that need to be reacted and the number of codon positions. Chemical reactions can be conducted by any means compatible with the presence of DNA including methods described herein and using methods referred in this document

The method described here, make use of iterative steps of subtraction of specifically formed duplexes between the anti-tags supplied and the corresponding identifier codon sequences. The method relies on efficient retrieval of the duplexes which can be done using any means useful for isolation of DNA duplexes. Consequently, any entity capable of being linked to an anti-tag and useful as handle for purification purposes may be used for for the allocation steps described herein. Specifically, the anti-tags may be supplied with a handle for purification of the duplexex, such as a biotin-group for interaction with streptavidine-beads or derivatives thereof, a dinitrophenol (DNP) for purification using DNP-specific antibodies (f.ex covalently attached to a solid-support) or having a chemical entity f. ex a thiol-group capable of reacting forming a covalent link with a solid-support such as 2-pyridin-activated thio-sepharose (Amersham Biosciences).
In principle, the anti-tag or pool of anti-tags may be linked covalently, or non-covalently to a solid-support prior to hybridization of the identifier templates.

Templated resynthesis

Step1: Construction of anti-tag columns

16 different twenty-base capture oligonucleotides were synthesized using standard phosphoramidite chemistry, with the addition of a C12-methoxytritylamine modifier at the 5'-end (Glen Research #10-1912, DNA technology, Aarhus Denmark). The HPLC purified oligonucleotides were loaded on a DEAE column and reacted with Fmoc-amino-PEG24 carboxylic-acid (Quanta BioDesign, ltd) using DMT-MM as activating agent. Excess Fmoc-Amino-PEG linker was removed by collecting the oligonucleotide on a DEAE column followed by Fmoc deprotection by two 1-ml treatments with 20% piperidine in DMF, one for 3 min and one for 17 min. Following elution from DEAE, the oligonucleotides were purified by microspin column gelfiltration (bio-rad) and analysed on ES-MS. The oligonucleotides were covalently attached to a sepharose resin by incubation with one volume equivalent of drained NHS-activated Sepharose (Amersham Biosciences #17-0906-01). The suspension was rotated at 37 °C ON before addition of

1M Tris-HCl and incubation ON. The product resin was washed and could be stored at 4 °C or – 20 °C.

The derivatized resins were loaded into empty DNA synthesis column housings (#CL-1502-1; Biosearch Technologies, Novato, California, United States).

Step 2: ssDNA template hybridization. Approximately 250 µl of DEAE Sepharose suspension was pipetted into an empty Glen Research column housing and washed with 20 ml of H_2O followed by 12 ml of DEAE bind buffer (10 mM acetic acid and 0.005% Triton X-100) using a syringe or a syringe barrel, a male-male luer adapter, and a vacuum manifold. The template DNA was loaded onto the washed chemistry column in 1 ml of DEAE bind buffer at approximately 1 ml/min. Anticodon columns were connected in series to the DEAE column using male tapered luer couplers, capillary tubing, silicone tubing, and tubing connectors. Approximately 3 ml of hybridization buffer containing 1 nmol of each oligonucleotide complementary to the noncoding regions was cyclically pumped over the system at 0.5 ml/min for 1 h at 70 °C, 10 min at 37 °C, and 1 h in a 46-°C water bath within a 37-°C room. Hybridized DNA was transferred back to fresh individual DEAE columns for loading of the specific reactants,

Step3: Chemical reactions at position A

Chemical reaction on the reactive amino-group on the template was carried out essentially as descrinbed in Halpin and Harbury (PLoS, 2004). To accomplish amino acid additions, columns were washed with 3 ml of DMF and subsequently incubated with 50 mM Fmoc protected-AA shown in table 1.4 and 50 mM DMT-MM in 100 ul of coupling mix containing 2% DEA in DIPEA/H2O (95:5) for 10 min. Excess reagent was washed away with 3 ml DMF, and the coupling procedure was repeated. The Fmoc-protecting group was then removed by two 1-ml treatments with 20% piperidine in DMF, one for 3 min and one for 17 min. Finally, the columns were washed with 3 ml of DMF followed by 3 ml of DEAE Bind Buffer (10 mM acetic acid, 0.005% Triton X-100). Identifier templates were eluted with 2 ml of Basic Elute Buffer

(1.5 M NaCl, 10 mM NaOH, and 0.005% Triton X-100) heated to 80 °C. The DNA was pooled, precipitated with ethanol/acetate, redissolved and reloaded on a fresh DEAE column.

Subsequent re-allocation according to codon B, C and D. Construction of anti-tag columns, ssDNA template allocation and transfer to specific DEAE columns for position B, C and D reactions was accomplished using the protocol described above for codon A.

Chemical reaction at position B

Building block reactants according to Table 1.4B was reacted using 50 mM of reactant, 50 mM DMT-MM in in 100 ul of coupling mix containing 2% DIPEA (N,N'-Diisopropyethylamin) in DMF/H2O (95:5) for 10 min. Excess reagent was washed away with 3 ml DMF, and the coupling procedure was repeated. The Msec protection group was removed by addition of 20% piperidine in H2O for 10 min. The process was repeated once.

Chemical reactions at position C

Building blocks (reactants) for position C is listed in Table1.4C

i) Acylation reactions: Conducted as described above.

ii) Isocyanate addition: The DNA on DEAE was washed with 0.5 ml of a buffer containing 100mM sodium borate and 100mM sodium phosphate pH 8.0 and subsequently incubated with 50 mM of specific isocyanate reactant in CH3CN in the above buffer in a total volume of 100 ul. The reaction was incubated at 50oC ON.

iii) Sulphonylation: The DNA on DEAE was washed using 100 mM Na-borate pH 9. Subsequently 10 ul of 100 mM of sulphonylation reactant in THF is mixed with 40 ul of 100 mM Na-borate buffer pH 9 and incubated at 30°C ON.

Following transformations all resins are washed and the templated molecules are Ns deprotected by incubation in a solution of 0.25 M mercaptoanisol and 0.25 M

DIPEA (N,N'-Diisopropylethylamine) in DMF and incubated ON at 25°C in an eppendorph thermoshaker at 600 rpm. Then the material on DEAE was washed with 0.3M AcOH in DMF, then twice with DMF before elution.

Chemical reactions at position D

Building blocks (reactants) for position D are listed in Table 1.4D

Acylation, isocyanate addition and sulphonylation was carried out as described above.

iv) Nucleophilic aromatic substitution: DNA on DEAE was washed once with 0.5 ml 100 mM Na-borate buffer pH 9.0. 25 ul of the reactant in (100 mM in DMSO) was mixed with 25 ul of 100 mM Na-borate pH 9.0 was added and the reaction incubated at 90 °C ON

v) Reductive amination: DNA on the DEAE resin was washed with 0.5 ml of 200 Na-acetate buffer pH 5.0 in 90 % DMF followed by incubation of 10 ul of 200 mM reactant in DMSO dissolved in 40 ul of 200 mM Na-acetate buffer pH 5.0 in 90 % DMF and subsequent incubation at 30 °C for 1 hour. Subsequently 25 ul of freshly prepared 140 mM $NaCNBH_3$ in Na-acetate buffer pH 5.0 was added followed by incubation ON at 30 °C

Following the final chemical reactions, all samples are subjected to an Fmoc deprotection reaction using piperidine as described above (position A). The DNA is eluted from the DEAE columns, pooled and precipitated using ethanol/acetate. Following centrifugation the pellet is washed twice with 70% ethanol, dried and redissolved in H_2O.

Prior to iterating the affinity selections on trombin, the singlestranded library of bifunctional molecules is converted to a doublestranded form by polymerase extension as described in example 1.

<u>A. An Exemplary Encoding Scheme</u>

The encoding scheme described below represents one of many different possible embodiments of the encoding schemes encompassed by the present invention in combination with the split-and-mix synthesis methods disclosed herein elsewhere. All of the possible encoding schemes that are encompassed under this invention are

based on differential hybridization to nucleic acid tags during a split-and-recombine synthesis.

1. The Solid Support.

In the present invention, the conventional solid support (typically a polystyrene/ polymethylacrylate bead, or a polyethyleneglycol hybrid thereof) has been replaced with a nucleic acid sequence.

In an exemplary embodiment the nucleic acid tag comprises or consists of at least 220 basepairs and more preferably contains 420 base pairs. In some cases the nucleic acid tag contains more than 420 base pairs.

In another exemplary embodiment the nucleic acid tag comprises or consists of from about 40 to 160 basepairs, such as from 60 to 80 basepairs, for example from 80 to 100 basepairs, such as from 100 to 120 basepairs, for example from 120 to 140 basepairs, such as from 140 to 160 basepairs. In some cases the nucleic acid tag contains more than 160 basepairs, such as more than 200 base pairs.

In one exemplary embodiment, the nucleic acid tag consists of 21 regions of twenty base pairs. Eleven of these regions are denoted C,- > C", wherein, C is an abbreviation for "constant" and refers to the "spacer" sequences described above. In this embodiment, the ten remaining regions are denoted V,- > V, o wherein, V is an abbreviation for "variable" and refers to the hybridization sequences which are different for each group of subsets of nucleic acid sequences. In this embodiment, every V region is bordered by two different C regions.

In one exemplary embodiment, the nucleic acid tag consists of 3 regions of twenty base pairs and 4 regions of ten nucleotides. The 4 regions of ten nucleotides are denoted C,- > C", wherein, C is an abbreviation for "constant" and refers to the "spacer" sequences described above. In this embodiment, the 3 regions of twenty nucleotides are denoted V,- > V, o wherein, V is an abbreviation for "variable" and refers to the hybridization sequences which are different for each group of subsets of nucleic acid sequences. In this embodiment, every V region is bordered by two different C regions.

In one exemplary embodiment, the nucleic acid tag consists of 4 regions of twenty base pairs and 5 regions of ten nucleotides. The 5 regions of ten nucleotides are denoted C,- > C", wherein, C is an abbreviation for "constant" and refers to the "spacer" sequences described above. In this embodiment, the 4 regions of twenty nucleotides are denoted V,- > V, o wherein, V is an abbreviation for "variable" and refers to the hybridization sequences which are different for each group of subsets of nucleic acid sequences. In this embodiment, every V region is bordered by two different C regions.

The pool of nucleic acid tags is degenerate, meaning that almost all of the nucleic acid tags differ from one another in nucleotide sequence. The nucleotide differences between different nucleic acid tags reside entirely in the hybridization sequences. For example, in one embodiment in the V, region, ten different twenty base-pair sequences are present. In another embodiment in the V, region, 100 different twenty base-pair sequences are present. Each unique twenty base-pair sequence can be referred to as a "ZIP code". Thus ten different" ZIP codes", denoted a,, b,, c,... j,, appear in the V, region of the different nucleic acid tags. Likewise, ten more unique"ZIP codes", denoted a2, b2, c2... j2, appear in the V2 region of the different nucleic acid tags. A third set of 10 or 100 unique ZIP codes appears in the V3 region, etc.

In this embodiment, all of the DNA tags share the same twenty base-pair sequence in designated spacer regions, i. e., the c, spacer region is denoted z,. A different 20 base-pair sequence, z2, appears in the C2 region of every DNA tag. Accordingly in an embodiment where the nucleic acid tag contains 420 base pairs, in regions C3- > C", all of the tags have the spacer sequences Z3- > Z, respectively.

Thus each 420 base pair nucleic acid tag consists of an ordered assembly composed of 111 different twenty base-pair reactants, the 100 ZIP codes (a"b"c,... d5, e5, 5,... hlo ilo, jio) and the 11 spacer regions (z,... z"). The 111 twenty base-pair reactants have the following properties: (i) micromolar concentrations of all 111 sequences hybridize to their complementary DNA sequences efficiently in solution at a specified temperature designated Tm, and (ii) the 111 sequences are orthogonal to each other with respect to hybridization, meaning that none of the 111 sequences cross-hybridizes efficiently with another of the 111 sequences, or with the complement to any of the other 111 sequences, at the temperature Tm.

The degenerated identifier oligonucleotides comprising a plurality of nucleic acid tags can be assembled from their constituent reactants e.g. by the primerless PCR assembly method described by Stemmer et al., Gene 164 (1): 49-53 (1995).

However, the identifier oligonucleotides comprising a plurality of tags can also be provided as described herein above by step-wise ligation of tags. In one embodiment of this method, both tags and anti-tags are ligated. In another embodiment, tags are ligated using one or more "splints" capable of hybridising to the tags to be ligated.

2. The Chemical Reaction Site

The 5'alcohol of the 5'base of the nucleic acid tag is modified with a commercially available reagent which introduces a phosphate group tethered to a linear spacer, e. g., a 12carbon and terminated with a primary amine group (e. g., Glen Research catalog#10-1912-xx or numerous other reagents which are available for introducing thiols or other chemical reaction sites into synthetic DNA).

The primary amine represents the chemical reaction site on which the compound library is synthesized. Many different types of chemical reaction sites (in addition to primary amines) can be introduced at the 5'terminus of the nucleic acid tag. Exemplary chemical reaction sites include, but are not limited to, chemical components capable of forming amide, ester, urea, urethane, carbon-carbonyl bonds, carbon-nitrogen bonds, carbon-carbon single bonds, olefin bonds, thioether bonds, and disulfide bonds. In the case of enzymatic synthesis, co-factors can be supplied as are required for effective catalysis. Such co-factors are known to those of skill in the art. An exemplary cofactor is the phosphopantetheinyl group useful for polyketide synthesis.

B. Carrying out a DNA-templated Split

The compound library can be split into subsets at each step of the split-and-recombine combinatorial synthesis by differential hybridization of the nucleic acid tag to complementary oligonucleotides or oligonucleotide analogs bound to a solid support, e. g., polystyrene beads.

In a preferred embodiment, the hybridization sequence of each nucleic acid tag

comprises at least 10 nucleotides.

The reagents described below are used to carry out the first step of an exemplary encoded split and are analogous to those used to carry out subsequent splits.

Oligonucleotides or oligonucleotide analogs which represent the complementary sequences to each of the hybridization sequences of the nucleic acid tags are synthesized. The 5' alcohols of the 5'bases of the each oligonucleotide or oligonucleotide analog are modified with a commercially available reagent which introduces a phosphate group tethered to a linear spacer, having for example six carbons and terminated with a thiol group (Glen Research catalog#10- 1926-xx). Each of the thiol-bearing oligonucleotides or oligonucleotide analogs is immobilized through a thioether linkage to a macroporous resin (e. g., polystyrene, MPS; Biopore catalog#NH-2CM, L-970317) bearing electrophilic bromoacetamide groups (the preparation of which is described below). Thus a number of affinity resins result, each bearing a unique oligonucleotide or oligonucleotide analog. Each of the affinity resins is loaded into its own column with luerlock fittings at either end and the columns connected in a linear sequence.

Numerous variants on the DNA encoding strategy, the attachment of chemical reaction sites to the DNA, and the specific chemistry or biochemistry used to construct the compound library are possible. Variation in the specific resins used to carry out the library splits, and to perform the chemical/biochemical coupling steps are also possible.

By way of application to the exemplary embodiment described above, the nucleic acid tag comprises 420 base pairs and 10 hybridization sequences. In this case, 10 different affinity resins and corresponding columns are used to form 10 subsets of nucleic acid sequences in each step of the synthesis of the compound library.

An exemplary first nucleic acid-encoded split is performed by contacting, i. e. pumping a high-salt aqueous solution containing the entire pool of different nucleic acid tags cyclically over the linear sequence of affinity columns under high stringency conditions [See, e. g., Southern, EM et al., Nucl Acids Res. 22 (8) 1368-1373 (1994)], using a peristaltic pump for a time sufficient for all of the specific hybridization sequences of each DNA to hybridize to the oligonucleotide or

oligonucleotide analogs bound to the columns. The DNA encoded split is completed simply by breaking the luer-lock linkages between the affinity columns. At this point the different DNA tags have been divided into physically separate subsets on the basis of the specific hybridization sequence in the V region of each tag.

To carry out the DNA-templated split for the second and subsequent synthetic steps, new affinity columns are prepared which display oligonucleotides corresponding to additional groups of different hybridization sequences bound to the polystyrene resin. These columns separate the DNA tags into additional subsets on the basis of which of possible nucleic acid sequences is present in the hybridization region of each nucleic acid tag. In a preferred embodiment at least 5 separate hybridization steps are preformed. In an even more preferred embodiment at least 10 separate hybridization steps are preformed.

The MPS resin described above is prepared from commercially available chloromethyl MPS resin in four steps (Biopore catalog#NH-2CM, L-970317): (i) the chloromethyl MPS resin is coupled to thioglycolic acid (ii) the N-hydroxy succinimide active ester of the coupled thioglycolic acid is prepared (iii) a Jeffamine 1500 molecular weight diamine (Fluke chemical#14535) is coupled to the resin by formation of an amide bond with the thioglycolic active ester (iv) the second amine of the coupled Jeffamine is acetylated with bromoacetic anhydride to produce the final bromoacetamide functionalized MPS resin.

Chemical Coupling

Each subset of nucleic acid tags formed by hybridization as described above is subjected to a different synthetic coupling reaction.

By way of example, a polypeptide can be formed by the methods of the present invention, as described below.

For synthesis of a polypeptide on the linker substrate in the direction of carboxy to amino terminus, a free amino terminus on the linker is required that can be conveniently blocked and deblocked as needed. A preferred amino terminus blocking group is a fluorenylmethoxycarbonyl group (FMOC).

For example, to couple an Fmoc-protected amino-acid to the to the primary amine

"chemical reaction site"which is covalently attached to the synthesis-directing nucleic acid sequence or tag, the following steps are carried out: (i) the DNA tags hybridized to the affinity columns are transferred onto columns, e. g., hydroxyapatite resin columns (Bio-Rad Macro-Prep Ceramic Hyroxyapatite TYPE II catalog#1588200) with elution in 300 M CaCl or DEAE Sepharose fas (Pharmacia 17-0709-01) with elution in 10mM acetate at pH 5.0 with 0.005% triton). The DNA tags remain non-covalently bound to the hydroxyapatite or sepharose resin in numerous organic solvents (for example DMF, acetonitrile, ethanol, and mixtures of those solvents with water). Thus organic reagents can be flowed over the columns and reacted with the chemical reaction sites on the DNA tags in the same manner that conventional solid phase chemical synthesis is carried out. Accordingly, a different Fmoc-protected amino-acid preactivated with N (lH-benzotriazol-1-yl) (dimethylamino) methylene-N-methylmethanaminium tetrafluoroborate (TBTU) or as an N-hydroxy succimnimide ester in DMF is flowed over each hydroxyapatite or sepharose column, resulting in the acylation of the primary amines of the DNA tags on each of the hydroxyapatite or sepharose columns with an Fmoc-protected amino acid [Albericio, F. and Carpino LA, Methods in Enzymology 289: 104-26 (1997)]. Following acylation, the Fmoc group is removed from the newly added amino acid by flowing a piperidine/DMF solution over the hydroxyapatite or sepharose columns, thus presenting a new primary amine ready for the next coupling step.

Numerous methods for modification of DNA are known to those of skill in the art and readily incorporated into the methods described herein [See, e. g., Chu, BC, et al. Nucleic Acids Research 11 (18): 6513-6529 (1983)]. By way of further example, nucleotides can be synthesized by various methods known to those of skill in the art. [See e. g.,"Oligonucleotide Synthesis: A Practical Approach", ed. M. J. Gait, JRL Press, New York, N. Y. (1990)].

An entire compound library is synthesized by carrying out alternate rounds of DNAtemplated library splitting and chemical and/or biochemical coupling to each subsets of nucleic acid tags.

The plurality of chemical compounds produced by the methods of the present invention are linked to nucleic acid sequence tags which facilitate identification of the chemical structure.

Conventional DNA sequencing methods are readily available and useful for a determination of the sequence of the synthesis-directing nucleic acid tags. See, e. g., Maniatis et al., eds, MOLECULAR CLONING: A LABORATORY MANUAL, Second Edition, Cold Spring Harbor, N. Y. (1989).

III. Selection, Amplification and Enrichment

The compound library can be screened for a desired activity, for example the ability to catalyze a particular reaction or to bind with high affinity to an immobilized receptor. In most cases, the subpopulation of molecules with the desired activity, as well as their nucleic acid tags, are physically partitioned away from siblings during the selection. Following selection, the nucleic acid tags attached to the selected molecules are amplified by the polymerase chain reaction [PCR] [Saiki et al, Science 239 (4839) 487-491 (1988)]. The 5'hydroxyl of the 5'-end primer used to PCR amplify the coding strand is modified with a phosphate group tethered to a fresh primary amine chemical reaction site. After amplification, the coding strand is separated from the non-coding strand. Because the nucleic acid tags direct the library synthesis in the present invention, rather than merely reporting on the synthetic history of individual compounds, the coding strands amplified from the first library can be used to direct the construction of a second generation compound library. Iteration of this procedure, by carrying out multiple rounds of selection, DNA tag amplification, and library resynthesis, allows individual desirable compounds to"evolve"from extremely complex libraries.

A. Screening Library for a Desired Activity

An entire compound library or individual library members produced by the methods of the present invention can be evaluated for one or more desired activities in screening assays capable of distinguishing compounds which modulate an activity or possess a desired structural or functional property.

Exemplary assays and functional analyses include, but are not limited to, enzymatic assays, non-enzymatic catalytic assays, protein-protein binding assays, receptor/ligand binding assays and cell-based assays. More specifically, exemplary cell-based methods provided by the present invention are based on; (1) differential binding of library compounds to a cell surface (i. e. binding to cancer cell and not a non-cancer cell), (2) binding of library compounds to components of a cell extract (e. g., binding to a cell fraction produced by separating an entire cell extract on a

sucrose gradient), (3) library compounds capable of endocytosis by a cell, and (4) in vivo localization and binding properties of library compounds by injecting the library into an animal. [See, e. g., Arap, W., et al., Science 279 (5349): 377-80. (1998) which describes in vivo selection of phage display libraries to isolate peptides that home specifically to tumor blood vessels
As will be appreciated by those of skill in the art, such assays can be preformed on entire libraries of compounds synthesized by the methods described herein or sub populations derived therefrom.

The number of possible receptor molecules for which ligands can be synthesized and identified by the methods of the present invention is virtually unlimited. Exemplary receptor molecules include, but are not limited to antibodies, growth factors, hormones, enzyme substrates, interferons, interleukins, intracellular and intercellular messengers, lectins, cellular adhesion molecules, and the like. Additional exemplary ligands include, but are not limited to, carbohydrates, non-protein organic compounds, metals, peptide mimetics, non-ribosomally produced polypeptides, conotoxins and polyketides, etc.

Desired compounds produced by the nucleic acid tag-directed combinatorial library methods of the present invention include, but are not limited to, small organic molecules, polyketides, subunit oligomers and catalysts for the synthesis of complex molecules from simple substrates, e. g., transition metal mediated reactions termed"domino"reactions which are highly efficient processes that allow for production of large libraries of complex structures in relatively few steps beginning with simple precursors. [See, e. g., Tietze and Lieb, Curr Opin Chem Biol 2: 63-371 (1998)].

B. In vitro Evolution Of Selected Compounds-Gene Shuffling
In addition to allowing amplification of selected library members, the present invention permits evolution of the encoded compound libraries. More specifically, genetic recombination between the nucleic acid tags which encode selected subpopulations of compounds is carried out in vitro by mutagenesis or random fragmentation of the nucleic acid tag sequence, followed by the generation of related nucleic acid sequences ["gene shuffling", Stemmer, Nature, 370: 389391 (1994); U. S. Patent No. 5,811,238 (1998)], and subsequent step-wise synthesis of additional compounds.

In one embodiment of the invention, a unique restriction site is introduced into each specific hybridization sequence. By way of example, partial digestion of a library with 11 specific hybridization sequences is accomplished by partial digestion with 11 corresponding restriction enzymes, followed by a primerless PCR reassembly reaction, allowing the nucleic acid tags for compounds that have been selected out of the library to be recombined with one another and further synthetic steps carried out. By analogy to gene shuffling for protein synthesis [Crameri, et al., Nature 391 (6664): 288-291 (1998)], the ability to carry out genetic recombination of compound libraries vastly increases the efficiency with which the diversity in the compound libraries can be explored and optimized.

Accordingly, the invention provides for polynucleotide shuffling to yield a population of variant nucleic acid sequences, capable of directing the synthesis of structurally-related, and/or functionally-related molecules, and/or variants thereof to create compounds having one or more desired activities. For example, molecules capable of binding to the 5'untranslated region (UTR) of mRNA can be identified in this manner.

It is also contemplated that the method of this invention can be used for the in vitro amplification of a selected subpopulations of synthesis directing nucleic acid tags by PCR, either prior to or following"gene shuffling".

General selection steps and further down-stream processing steps

Once a library of bifunctional complexes have been synthesised it is possible to select and/or screen and/or partition and/or purify the library in order to identify or isolate desirable compounds therefrom. The compounds in one embodiment are small scaffolded molecules.

The partitioning may be based one or more features or properties of a molecule. Such a feature may be associated with or reside in a bifunctional molecule or a part of or a combination of parts of the encoded small molecule, the linker, the identifier. Partitioning may be based a structural, chemical, or electronic feature of a molecule. Partitioning may be based on a feature of a molecule or one or more parts of the molecule such as affinity for a target, hydrophobicity, hydrophilicity, charge distribution, size, mass, volume, conductivity, electric resistance, reactivity under

certain conditions such as bond formation to a target, effect of the molecule such as induction of a signal in a system, e.g. a biochemical system, a biological system such as cell or a whole organism. The feature may be present in the molecule or it may be induced by the addition of a cofactor, e.g. a metal ion to the molecule.

A number of screening methods exist, for the identification of molecules, e.g. organic molecules such as the encoded molecule part of a bifunctional complex or the tag part of a bifunctional complex, with desired characteristics. Different types of selection or screening protocols are described in (Rasmussen (2006) WO 06/053571A2, Liu et al. (2002), WO 02/074929 A2; Pedersen et al. (2002) WO 02/103008 A2; Pedersen et al. (2003) WO03/078625 A2; Lerner et al., EP 0643778 BI, Encoded combinatorial chemical libraries; Dower et al., EP 0604552 BI; Freskgard et al., WO 2004/039825 A2; Morgan et al., 2005, WO 2005/058479; Harbury and Halpin, WO 00/23458). For example, affinity selections may be performed according to the principles used in library-based selection methods such as phage display, polysome display, and mRNA-fusion protein displayed peptides. The template-directed synthesis of the invention permits selection procedures analogous to other display methods such as phage display (Smith (1985) SCIENCE 228: 1315- 1317). Phage display selection has been used successfully on peptides (Wells et al. (1992) CURR. OP. STRUCT. BIOL. 2: 597-604), proteins (Marks et al. (1992) J.BIOL. CHEM. 267: 16007- 16010) and antibodies (Winter et al. (1994)ANNU. REV. IMMUNOL. 12: 433-455). Similar selection procedures also are exploited for other types of display systems such as ribosome display Mattheakis et al. (1994) PROC. NATL. ACAD.Sci. 91: 9022-9026) and mRNA display (Roberts, et al. (1997) PROC. NATL. ACAD.Sci. 94: 12297-302).

The invention also relates to a method for identifying a molecule having a preselected property, comprising the steps of: subjecting the library produced according to the method indicated above to a condition, wherein a molecule or a subset of molecules having a predetermined property is partitioned from the remainder of the library, and identifying the molecule(s) having a preselected function by decoding the identifier oligonucleotide of the complex.

The above method, generally referred to as selection or screening, involves that a library is subjected to a condition in order to select molecules having a property which is responsive to this condition. The condition may involve the exposure of the

library to a target. The bifunctional complexes having an affinity towards this target can be partitioned form the remainder of the library by removing non-binding complexes and subsequent eluting under more stringent conditions the complexes that have bound to the target. Alternatively, the identifier oligonucleotide of the bifunctional complex can be cleaved from the molecule after the removal of non-binding complexes and the identifier oligonucleotide can be recovered and decoded to identify the molecule.

Specific screening methods employing bifuntional molecules for the identification of organic molecules with desired characteristics include but are not limited to:

i. Affinity selection on immobilised target molecules. In this approach the target molecules (e.g., DNA, RNA, protein, peptide, carbohydrate, organic or inorganic molecule, supramolecular structure or any other molecule, is immobilized covalently or non- covalently to a solid support such as beads, the bottom of a well of a microtiter plate, a reagent tube, a chromatographic column, or any other type of solid support. A library of bi-functional molecules are now incubated with the immobilized target molecule, excess non-bound bi-functional molecules are washed off by the replacing supernatant or column buffer with buffer not containing bi-functional molecules one or more times. After washing the bound bi-functional molecules are released from solid support by addition of reagents, specific ligands or the like that results in the elution of the bi-functional molecule, or the pH is increased or decreased to release the bound bi-functional molecules, or the identifier of the bi-functional molecule, e.g., one or both strands of the identifier, is released from the encoded molecule with a reagent, pH change or light-induced cleavage. The recovered identifiers can now optionally be amplified by PCR, optionally cloned and sequenced to reveal the structure of the ligands encoded by the identifier. As an alternative, the identifiers or bi-functional molecules comprising identifiers, are not released from solid support, but rather the identifiers are optionally amplified by PCR and/or analyzed directly while still immobilised on solid support. Selection of binding molecules from a library can be performed in any format to identify optimal binding molecules. Binding selections typically involve immobilizing the desired target molecule, adding a library of potential binders, and removing non-binders by washing. When the molecules showing low affinity for an immobilized target are washed away, the molecules with a stronger affinity generally remain attached to the target. The enriched population remaining bound to the

target after stringent washing is preferably eluted with, for example, acid, chaotropic salts, heat, competitive elution with a known ligand or by proteolytic release of the target and/or of template molecules. The eluted templates are suitable for PCR, leading to many orders of amplification, whereby essentially each selected template becomes available at a greatly increased copy number for cloning, sequencing, and/or further enrichment or diversification. In a binding assay, when the concentration of ligand is much less than that of the target (as it would be during the selection of a DNA-templated library), the fraction of ligand bound to target is determined by the effective concentration of the target protein.The fraction of ligand bound to target is a sigmoidal function of the concentration of target, with the midpoint (50% bound) at [target] = Kd of the ligand-target complex. This relationship indicates that the stringency of a specific selection-the minimum ligand affinity required to remain bound to the target during the selection-is determined by the target concentration. Therefore, selection stringency is controllable by varying the effective concentration of target. The target molecule (peptide, protein, DNA or other antigen) can be immobilized on a solid support, for example, a container wall, a wall of a microtiter plate well. The library preferably is dissolved in aqueous binding buffer in one pot and equilibrated in the presence of immobilized target molecule. Non-binders are washed away with buffer. Those molecules that may be binding to the target molecule through their attached DNA templates rather than through their synthetic moieties can be eliminated by washing the bound library with unfunctionalized templates lacking PCR primer binding sites. Remaining bound library members then can be eluted, for example, by denaturation. The target molecule can be immobilized on beads, particularly if there is doubt that the target molecule will adsorb sufficiently to a container wall, as may be the case for an unfolded target eluted from an SDS-PAGE gel. The derivatized beads can then be used to separate high-affinity library members from nonbinders by simply sedimenting the beads in a benchtop centrifuge. Alternatively, the beads clan be used to make an affinity column. In such cases, the library is passed through the column, one or more times to permit binding. The column then is washed to remove nonbinding library members. Magnetic beads are essentially a variant on the above; the target is attached to magnetic beads which are then used in the selection. There are many reactive matrices available for immobilizing the target molecule, including matrices bearing -NH2 groups or -SH groups., The target molecule can be immobilized by conjugation with NHS ester or maleimide groups covalently linked to Sepharose beads and the integrity of known properties of the target molecule can

be verified. Activated beads are available with attachment sites for-NH2 or-COOH groups (which can be used for coupling). Alternatively, the target molecule is blotted onto nitrocellulose or PVDF. When using a blotting strategy, the blot should be blocked (e. g., with BSA or similar protein) after immobilization of the target to prevent nonspecific binding of library members to the blot.

ii. Affinity selection on target molecules in solution, followed by any means of isolation of the bi-functional molecules bound to the target, e.g. by immunoprecipitation of the target-bi-functional molecule complexes, capture of the complexes on nitrocellulose filter or by immobilisation of the target via a functionality on the target such as biotin or GST-tag or Histidine-tag or other useful means for immobilization as recognized by a person skilled in the art. A library of bi-functional molecules are incubated with target molecules (e.g. a protein). After complex formation of bi-functional molecules with target, the complex is isolated from non-complexes, for example by the addition of polyvalent antibodies against the target molecule and precipitation of antibody-target-bi-functional molecule complexes, or is precipitated by the addition of beads that bind the target molecules. The latter may for example be by addition of streptavidin-coated beads that bind to pre-biotinylated targets. The identifiers recovered by precipitation can now be characterised or amplified, e.g., by PCR, as described in (i). The sequence of the identifiers will reveal the identity of the encoded molecules that bind the target molecules.

iii. Affinity selection on target molecules in solution, followed by gel retardation, chromatographic separation e.g. size exclusion chromatography, or separation by centrifugation e.g. in a $CsCl_2$-gradient. A library of bi-functional molecules are incubated with target molecules (e.g. a protein). After complex formation of bi-functional molecules with target, the complex is isolated from non-complexes, for example by gel electrophoresis or size exclusion chromatography, or any other chromatographic or non-chromatographic method that separates the target-bi-functional molecule complexes from non-complexed bi-functional molecules, for example based on the difference in size and/or charge. The tags of the bi-functional molecules of the column fraction or band on the gel that comprises target-bi-functional molecule complexes are now characterised or amplified, e.g., by PCR, as described above. The sequence of the tags will reveal the identity of the encoded molecules that bind the target molecules.

iv. Affinity selection on surfaces. Particles, preferably small particles, of solid material, e.g., metal particles, metal oxide particles, grinded plastic, wood, preformed carbon nanotubes, clay, glas, silica, bacterial biofilm or biofilm of other microorganism, cement, solid paint particles, laminate, stone, marble, quartz, textile, paper, skin, hair, cell membranes, industrial membranes, epiderm, or the like, is added to a solution comprising a library of bi-functional molecules. After incubation, one or more washing steps are performed, to remove unbound bi-functional molecules. Then, the bi-functional molecules bound to the surface, or the identifiers of the bi-functional molecules bound to the surface, are released as described above, and the identifiers characterised and/or amplified as described above.

v. Selection for intracellularisation. Bi-functional molecules are incubated with cells or micelles, or on one side of a lipid membrane, or on one side of a cell monolayer (e.g. CaCo2 cell monolayer), in order to allow the bi-functional molecule to pass or become immobilized into the membranes. Then, a number of washing steps are performed in order to remove bi-functional molecules that have not become immobilized or have passed the membrane. Identifiers from bi-functional molecules that have become immobilized or have passed the membrane are now amplified and/or characterized as described above.The encoded molecule of bi-functional molecules that have either become immobilized in the membrane or have passed the membrane, represent potential transporters for intracellularization, i.e. by attaching these encoded molecules (without the oligonucleotide tag) to e.g. non-oral drugs these may become orally available, because the transporter mediate their transport across the cell.

vi. Selection by phase partitioning. A two- or three phase system may be set up, wherein the bi-functional molecules will partition out according (at least in part) to the characteristics of the encoded molecules. Therefore, the principle allows the identification of encoded molecules that have particular preference for a certain kind of solvent. Again, the identifiers of the isolated bi-functional molecules can be amplified and/or characterised after the selection has occurred. It may be necessary to coat the nucleic acid component of the bi-functional molecule with e.g. DNA binding proteins, in order to ensure that the partitioning of the bi-functional molecule is significantly correlated with the characteristics of the encoded molecule of the bi-functional molecule.

vii. Selection for induced dimerisation of target molecules. In a preferred embodiment, encoded molecules are sought that induce the dimerization of target molecules. For example, small molecules with the potential to induce dimerization of protein receptors in the cell membrane may be applicable as therapeutics. Thus, a selection protocol for encoded molecules with the potential to induce dimerization of proteins A and B is as follows: A library of bi-functional molecules are incubated with proteins A and B. After incubation, the solution is applied to gel electrophoresis, ultracentrifugation (e.g. CsCl-centrifugation), size exclusion chromatography, or any other kind of separation that separates the protein A-protein B-bi-functional molecule-complex from un-complexed protein A and B, and other undesired complexes, such as protein A-protein B-complex. Bi-functional molecules from the band or fraction corresponding to the size and/or charge of the protein A-protein B-bi-functional molecule-complex is recovered, and template identifiers are then amplified and/or characterised as described above. In this case, the encoded molecule would be resynthesized, and tested in a protein dimerisation assay for its effect on the dimerisation of protein A and B.

viii. Selection by iterative rounds of binding and elution. This is a modification of the methods reported previously (Doyon et al. (2003), J. Am. Chem. Soc., 125, 12372-12373, the content of which is incorporated herein by reference in its entirety). Bi-functional molecules are incubated with e.g. immobilised target molecule, e.g. a biotinylated enzyme immobilised on streptavidin beads. After washing one or more times, the bound bi-functional molecules are released from solid support by a change in pH, addition of a detergent such as SDS, or by addition of an excess of ligand that binds the target molecule (the ligand can be e.g. a small molecule, peptide, DNA aptamer or protein that is known to bind the target molecule). Alternatively, the bi-functional molecules may be released by degradation of the immobilised target (e.g. by nuclease or protease), denaturation of target by methods such as heat or induced conformational changes in target structure or the like. The recovered bi-functional molecules are now re-applied to e.g. immobilised target molecule, optionally after removal or degradation of the ligand or reagent used for elution in the previous step. Again, washing is performed, and the bound bi-functional molecules eluted. The process of incubation and binding, washing and elution can be repeated many times, until eventually only bi-functional molecules of high affinity remains. Then the tags of the bi-functional molecules are amplified

and/or characterised. Using this kind of iterative binding and elution, enrichment factors higher than 1.000.000-fold can be obtained.

Targets may be immobilised on columns, on beads (batch selection), on the surface of a well, or target and ligands may interact in solution, followed by immunoprecipitation of the target (leading to immunoprecipitation of ligands bound to target). In one embodiment of iterative library partioning step(s) the target concentration is kept constant at all selection steps. In another embodiment it may be desirable to change the target concentration between or during each or some partitioning steps. Consequently, the experimenter can choose the affinity thresholds for molecule recovery based on the molecules affinity for the target by altering the target concentration. F. ex a first selection step may employ a target concentration in the range of 1-50 uM (or even higher if practically allowed). Following selection and isolation of the library pool enriched for ligands the library pool is incubated with a target in reduced concentration such as in the range of 0.01 – 5 uM. A reduction in target concentration will enable the experimenter to increase the recovery of the best ligands in a library compared to molecules of lower affinity thereby achieving a better or more exact ranking of isolated ligands from the library pool based on ligand affinity (i.e the number of specific DNA-tags isolated from the selection output correlate directly with molecule affinity for the target). In yet another embodiment, the ranking of ligands in a selection output is based on the off-rate of the target-molecule pair. Following the library incubation with immobilised target a specific ligand is added which saturate unbound target thus preventing rebinding of library molecules once released from it target binding site. This enables the experimenter to isolate library fractions eluted at different timepoints after target saturation resulting in primarily the isolation of molecules according to their off-rates (koff).

It is possible to perform a single or several rounds of selection against a specific target with a subsequently amplification of the selected variants. These obtained variants are then separately tested in a suitable assay. The selection condition can be stringent and specific to obtain binding molecules in one selection rounds. It can be advantageously to perform the method using a single round of selection because the number and diversity of the potential binders are larger compared to procedures using further selections where potential binders can be lost. In another embodiment the selection procedure involves several round of selection using increasing

stringency conditions. Between each selection an amplification of the selected complex can be desirable.

x. Whole organism selection. A library of bi-functional molecules, optionally modified by e.g. coating proteins, is injected into a dead or living animal, for example a mouse. After incubation for a period of time (e.g two hours) in the animal, specific tissue or organs are recovered, and the bi-functional molecules associated with specific organs can be characterised, by e.g. PCR amplification and/or sequencing of the corresponding identifiers. As a specific example, a mouse carrying a tumor can be injected with a library of bi-functional molecules. After incubation, the tumor can be isolated from the animal. The bi-functional molecules associated with the tumor are potential therapeutics or diagnostics for that cancer.

The abovementioned target molecules may be any supramolecular structure (e.g. nanoclusters, multiprotein complex, ribosomes), macromolecule (e.g. DNA, RNA, protein, polymers such as carbohydrates, thiophenes, fibrin), or low molecular weight compound (e.g. cAMP, small peptide hormones, chelates, morphine, drug). After having performed any of the selections above, the identifiers can taken through one more round of the same or another selection protocol. This process can be repeated until an appropriately small number of different bi-functional molecules are recovered.

The selection may be performed in the presence of one or more specific ligands for site on a target. For example, if it is desired to avoid identification of ligands to a particular target site, known ligands to that site may be included during selections. The known ligand may then compete with bifunctional molecules for binding to the particular site thus reducing or eliminating binding of bifunctional molecules to the site. In this way, the bifunctional molecules will not be identified based on their with affinity to the particular target site.

After having performed any of the selections above, the tags of the output bi-functional molecules can be amplified by PCR or other means, sequenced and the chemical composition of the molecule identified..

Polyvalent display and other means of increasing the likelihood of identifying encoded molecules with weak characteristics.

Under certain conditions the requirements of an encoded molecule, in order to be isolated during the screening step, are too strong, and few or none of the encoded molecules of a library are expected to fulfil the requirements. Such requirements may be for example high affinity or high catalytic turn-over. The methods and success of multivalent display in affinity selections is evident from systems similar to that described here such as phage display as should be recognized by persons skilled in the art

Thus, it may be desirable to employ a multivalent display mode, i.e., to generate libraries of multivalent encoded molecules (multiple encoded molecules attached to one tag). During a selection step in which for example an encoded molecule interacts weakly with a target protein, a multivalent encoded molecule may interact with multiple protein targets through the multiple copies of encoded molecules that it contains, and as a result, may bind with higher affinity because of the avidity effect. Likewise, in a screening or selection step for catalytic efficiency, a multivalent encoded molecule may generate more product in a given time, and may be isolated because of this.

A preferred means of generating libraries of multivalent encoded molecules each containing multiple copies of the same encoded molecule, is as follows: The DNA tag-piece (denoted "Display oligonucleotide" or "single-stranded identifier") employed for chemical reaction can be synthesised with 1 or more reactive handles using standard phosphoramidite chemistry. One strategy for the introduction of multivalent display involves the incorporation of doublers or treblers (such as Glen Research catalog No10-1920-90 or 10-1922-90) one or more times forming dendrimer structures that can be capped by reactive handles f.ex amino-, acid-, Thiol- or aldehyde-group (or any chemical entity useful as starting point in a chemical reaction. This enables the formation of a single DNA sequence connected to any number of reactive handles such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 ,20 or more reactive handles. Figure 53 shows 3 examples of a simple quadruple amino-DNA tag enabling synthesis and display of the same encoded molecule attached to a single encoding tag. It may be desirable to include spacing groups such as polyethylene glycol (PEG) units at any point in the synthesis process (chosen by the experimenter) for improved synthesis and display of the synthetic molecule.

The multivalent encoded molecules can now be used in various screening or selection processes. For example, the multivalent encoded molecules may be added to an affinity column, to which target protein has been immobilised with an appropriately high density, so that multivalent encoded molecules may interact with several immobilised targets simultaneously. This will lead to the isolation of bi-functional molecules that contain encoded molecules with affinity for the immobilised target protein. The use of multivalent encoded molecules may be particularly advantageous to use when selecting for affinity to a homodimeric target molecule, or any other target that contains two or more identical binding sites. Relevant targets include membrane proteins such as the Epo-receptor, p53, HER2, Insulin Receptor, many interleukins, palindromic DNA- or RNA-sequences, or fibrin. Divalent encoded molecules containing identical encoded molecules are also appropriate for affinity selection on target molecules with one binding site, where the binding site is partly or fully symmetrical, and therefore allows two identical encoded molecules to interact.

In another embodiment the addition of a helper element comprising a helper molecule known to interact with the target, is linked to an oligonucleotide capable of hybridizing to a region on the DNA portion of the bi-functional library molecules may aid the isolation of a bifunctional molecule e.g. by increasing the overall affinity of the helper molecule/bifunctional molecule complex for the target. Figure 54 depicts a scheme for the addition, by hybridization, of a helper molecule covalently linked to a DNA sequence complementary to the region of DNA of the bifunctional library molecule that is proximal to the displayed molecule. Hybridization of a second primer followed by polymerase extention and ligation will produce dsDNA displaying both the encoded library molecule and the helper molecule

Consequently, if a ligand is known for a binding site in a protein, this ligand may be coupled to the bi-functional molecule, in order to guide the encoded molecule to the target protein, and in order to increase the affinity of the bi-functional molecule (carrying the known ligand) for the target protein Similar approaches may be used for isolation of encoded molecules with affinity for a target binding site, where the binding site can be occupied by both the encoded molecule and the known ligand simultaneously. Finally, it may be desirable to increase the overall affinity of the bi-functional molecule for the target by linking a short oligonucleotide that is

complementary to the tag of the bi-functional molecule to the target. The short oligonucleotide will then function as a helper moiety that increases the affinity of the bi-functional molecule for the target, by hybridisation of the short oligonucleotide to the bi-functional molecule.
Selections employing such bi-functional molecules to which have been attached a helper moiety may be applied to affinity selection against all kinds of targets, including protein-heterodimers as well as protein-homodimers, and thus molecular targets include HER2, Insulin-receptor, VEGF, EGF, IL-4, IL-2, TNF-alpha, the TATA-box of eukaryotic promoter regions, and many others.

In another embodiment, a target and the bifunctional molecules may be modified to allow screening. For example, an –SH group may be introduced in a protein target by mutagenesis of an amino acid to a cysteine. Correspondingly, a library of bifunctional molecules may be synthesized such that encoded molecules carry an –SH group. Alternatively, a library may following synthesis be reacted with a reactant that carries an –SH group. Screenings may then be performed under conditions that induce the formation of an S-S bond between the –SH of the target and the –SH of the encoded molecules of the library. In this way, the bifunctional molecules may be directed to a specific site on the target.

Dynamic combinatorial library of dimers or trimers of encoded molecules.
The bi-functional molecules of a library may be designed in a way that leads to transient complex formation between 2, 3, or more bi-functional complexes during the screening process. This may be desirable, especially in cases where the libraries that have been generated are relatively small, or in cases where it is desirable to screen a large number of combinations of encoded molecules for synergistic effects. In order to generate transient complexes, the bi-functional molecules may be designed so as to comprise half of a transient interaction pair. For example, a short single stranded oligonucleotide region may be included in the design of the tag of the bi-functional molecules ;if some of the bi-functional molecules carry a molecular entity “A” and some other bi-functional molecules of the library carry another molecular entity “B” that interacts transiently, i.e. forms a short-lived complex with, “A”, then the two sets of bi-functional molecules of the library will form transient dimers of bi-functional molecules. These transient dimers may then be exposed to a screening process, for example affinity selection, where the dimers are then examined for ability to bind to a certain target. As an example, for each of

the species of bi-functional molecules, half of the generated bi-functional molecules carry the oligo sequence 3'-ATGC-5' in the proximity of the encoded molecule, and the other half of the generated bi-functional molecules carry the oligo sequence 3'-GCTA-5'. When all the generated bi-functional molecules are incubated at appropriately low temperature, different combinations of dimers will transiently form, and allow for a feature displayed by the combination of the corresponding two encoded molecules to be selected for. This feature could be the binding of the two encoded molecules of the dimer to bind simultaneously to a target molecule. If appropriately designed, trimers may be (transiently) formed, by formation of triplex DNA between three bi-functional molecules. In this way, all the possible dimers (or trimers) of a pool of bi-functional molecules may be screened for the desired feature.

Once the screening of a library of bi-functional molecules has been done, the isolated bi-functional molecules may be identified. This can be done without DNA amplification or more preferably by use of PCR or other means of DNA amplification. Next, the structure of the molecules isolated can be identified from the tag sequence directly using techniques such as pyrosequencing described by Margulies, M. et al (Nature. 2005 Sep 15;437(7057):376-80) and incorporated herein by reference or by a probing technique described in WO2005093094 or other means of direct sequencing without cloning. Alternatively the tags can be cloned and sequenced by conventional means such as Sanger sequencing, mass spectrometry-based sequencing, single molecule sequencing, or sequencing by hybridisation to oligonuclotide arrays.

The characteristics of the encoded molecules thus identified may now be analyzed, either in its free form (after resynthesis by organic chemistry or after generation of the bi-functional molecule followed by cleavage of the linker that connects the encoded molecule and its identifier) or in its oligonucleotide-linked form (as a bi-functional molecule).

QC of library generation.

It may be desirable to test reaction efficiencies for the entire set- or a subset of chemical reactions. A simple method for evaluation of transformations efficiency is the use of Mass spectroscopy for analysis of library transformations. Consequently, a small sample of all reaction wells, a subset or of single wells may be collected and

analysed directly by any analytical tool available such as MALDI-TOF MS or Electrospray MS. Alternatively the sample may be subjected to a number of methods for the aid of the analysis. In one embodiment it may be desirably to purify the identifier from unwanted DNA, chemical entities, buffers etc using methods such as HPLC/FPLC, gelfiltration, Ion-chromatography, Gel-electrophoresis or using immobilisation on solid-support followed by elution of the library product. Subsequently, the identifier DNA can be analysed using spectroscopic methods including but not limited to MALDI-TOF or ES-MS.

In some embodiments it may be necessary to apply additional methods for the simplification of the analytical step. Since each bifunctional molecules generated by the library generation process contains both a DNA part and a chemical part, all samples following the first pool event comprises both a heterogeneous DNA part (due to the sequence differences) and heterogeneous chemical part due the differences in the chemical composition. Consequently, in order to analyze the chemical reactions it may be desirable to separate the DNA portion of the bifunctional molecule from the chemical entity. Thus, one method for separation is the use of a selectively cleavable linker connecting the DNA and the small molecule allowing cleavage and subsequent (optional) removal of the DNA allowing analysis of the remaining chemical fragment.

Selectively cleavable linkers have been described elsewhere and are incorporated herein by reference Pedersen (Pedersen et al. (2002) WO 02/103008 A2). One example is the use of a photo-cleavable linkers or the use of chemically labile linkers such as a linker comprising and S-S bond which can be selectively cleaved by reducing agents such as DTT or TCEP.

In an alternative approach, a fixed DNA sequence of the DNA-tag that separates the chemical entity from the heterologous DNA encoding part may contain a restriction site recognized by a DNA restriction endonuclease. Consequently, DNA cleavage would produce a sample containing a small uniform DNA segment connected to a heterologous chemical entity. This fragment may be purified by several methods which include but is not restricted to gel-eletrophoresis , HPLC or hybridization to a biotinylated DNA-oligonucleotide complementary to the DNA segment comprising the pool of chemical fragments followed by binding to streptavidine beads (SA-beads) and subsequent elution of the DNA fragments.

The example described below is included to describe one principle for the evaluation of transformation efficiencies during the generation of a library of bifunctional molecules: The example is used to illustrate one principle for quality control on one or more single reactions, a subset pool of reactions or a sample pool collected from all reactions

In a split and mix library generation procedure n chemical reactions are conducted producing n chemical fragments linked to N different tags producing intermediates with a common structure depicted in figure 55.

The procedure depicted in figure 55 can be conducted at each round of chemical reaction to monitor reaction efficiencies. If any reactions is not run satisfactorily, all or only a subset of reactions can be iterated and subject to another round of analysis. Such a process using chemical reactions followed by QC on the transformation rates can be repeated any number of time until sufficient chemical turn-over is achieved and verified.
For some analysis it may be desirable to purify the sample by gel-electrophoresis or other means such as to harvest the ssDNA or dsDNA identifier comprising the chemical entity and purify this moiety from the remaining DNA in the sample such as unligated surplus tags. Alternatively it may be desirable to purify a singlestranded form of the identifier f. ex by gel–electrophoresis on UREA-PAGE prior to step2 described above.

Another method for monitoring transformation efficiencies in library generation is to include one or more library mimics, a DNA molecule with a reactive entity, in the library synthesis step(s) containing a specific DNA sequence preferably unrelated to any sequence used for library tagging. The one or more mimics can be included as tracers to monitor single-, a subset pool or the entire pool of reactions at any synthesis or deprotection step during library generation. The mimics will be chemically transformed similar to the reactive entity on the identifier in the library generation process and can be included at any specific reaction step or at multiple reaction steps. As each mimic contains a unique DNA sequence, one or more mimics can be specifically subtracted from the library at any step and analysed for chemical transformations. This allows the experimenter to continuously analyse the chemical reaction within the library synthesis by examination of the included control

mimics. The methods for mimic isolation includes, but is not limited to, purification by UREA-PAGE, HPLC/FPLC or purification using binding to a complementary nucleic acids strand, PNA, LNA or molecule with equivalent specific hybridization function, that carries a handle, such as a biotin group, useful for purification such as on SA-beads as described above (Figure 56). Subsequently the mimics can be analysed by any suitable analytical tool such as MALDI- or Electrospray MS.

An alternative method for the purification of the control mimics in the library is to include a selective cleavable linker connecting a handle for purification and the reactive chemical unit. Figure 57 depicts the general principle. The reactive unit (site) is any suitable reactive groups for example but not limited to an amino, thiol, carboxylic- acid or aldehyd-group. The oligonucleotide moiety is optional but provides an excellent handle for molecular weight analysis using MS. The cleavable linker (optionally) is selectively cleavable by any means such as e.g. by enzymatic, chemical or photocleavable methods. The purification (optional) may be any unit capable of being selectively recovered.

Templated synthesis:

In some embodiments it may be desirable to amplify, by PCR or other means, the tags recovered from a selection step and use the amplified material as template for a subsequent synthesis of a library of bifunctional molecules. Methods for templated synthesis of bifunctional molecules include, but is not restricted to methods disclosed in (Rasmussen (2006) WO 06/053571A2, Liu et al. (2002), WO 02/074929 A2; Pedersen et al. (2002) WO 02/103008 A2; Pedersen et al. (2003) WO03/078625 A2; Harbury and Halpin, WO 00/23458, and further methods described herein. Alternatively the amplified tags may be used for the partitioning of a library of bifunctional molecules prior to selection on a target. This step will enrich a subset of the library by hybridization with the matching tag and the selection procedure(s) can be iterated with this library subset.
Such pre-selection partitioning of libraries of bifunctional molecules can be accomplished by various methods which include but is not restricted to techniques disclosed in Brenner and Lerner (1992, Proc, Natl. Acad. Sci 89:5381-83 Lerner et al., EP 0643778 B1; EP 0604552 B1; WO2004099441)

The templated library re-synthesis or subset partitioning followed by selection and amplification (optional) step(s) described above may be iterated any number of

times. Preferably, the processes are iterated until sufficient sequence bias is achieved for easy identification of ligands form tag sequencing.

The characteristics of the encoded molecules thus identified may now be analyzed, either in its free form (after resynthesis by organic chemistry or after generation of the bi-functional molecule followed by cleavage of the linker that connects the encoded molecule and its identifier) or in its oligonucleotide-linked form (as a bi-functional molecule).

Once the library has been formed in accordance with the methods disclosed herein, one must screen the library for chemical compounds having predetermined desirable characteristics. Predetermined desirable characteristics can include binding to a target, catalytically changing the target, chemically reacting with a target in a manner which alters/modifies the target or the functional activity of the target, and covalently attaching to the target as in a suicide inhibitor. In addition to bioactive species produced as disclosed herein above, bioactive species prepared in accordance with method A and B below, can be screened according to the present invention.

A. Molecules can be single compounds in their final "state", which are tagged individually and separately. E.g. single compounds may individually be attached to a unique tag. Each unique tag holds information on that specific compound, such as e.g. structure, molecular mass etc.

B. A molecule can be a mixture of compounds, which can be considered to be in their final "state". These molecules are normally tagged individually and separately, i.e. each single compound in a mixture of compounds can be attached to the same tag. Another tag can be used for another mixture of compounds. Each unique tag holds information on that specific mixture, such as e.g. spatial position on a plate.

The target can be any compound of interest. The target can be a protein, peptide, carbohydrate, polysaccharide, glycoprotein, hormone, receptor, antigen, antibody, virus, substrate, metabolite, transition state analog, cofactor, inhibitor, drug, dye, nutrient, growth factor, cell, tissue, etc. without limitation. Particularly preferred targets include, but are not limited to, angiotensin converting enzyme, renin, cyclooxygenase, 5-lipoxygenase, IIL- 1 0 converting enzyme, cytokine receptors,

PDGF receptor, type II inosine monophosphate dehydrogenase, ß-lactamases, and fungal cytochrome P-450. Targets can include, but are not limited to, bradykinin, neutrophil elastase, the HIV proteins, including *tat, rev, gag, int,* RT, nucleocapsid etc., VEGF, bFGF, TGFß, KGF, PDGF, thrombin, theophylline, caffeine, substance P, IgE, sPLA2, red blood cells, glioblastomas, fibrin clots, PBMCs, hCG, lectins, selectins, cytokines, ICP4, complement proteins, etc. The target can also be for example, a surface (such as metal, plastic, composite, glass, ceramics, rubber, skin, or tissue); a polymer; a catalyst; or a target biomolecule such as a nucleic acid, a protein (including enzymes, receptors, antibodies, and glycoproteins), a signal molecule (such as cAMP, inositol triphosphate, peptides, or prostaglandins), a carbohydrate, or a lipid. Binding assays can be advantageously combined with activity assays for the effect of a reaction product on a function of a target molecule.

The libraries of the present invention can contain molecules that could potentially bind to any known or unknown target. The binding region of a target molecule could include a catalytic site of an enzyme, a binding pocket on a receptor (for example, a G-protein coupled receptor), a protein surface area involved in a protein-protein or protein-nucleic acid interaction (preferably a hot-spot region), or a specific site on DNA (such as the major groove). The natural function of the target could be stimulated (agonized), reduced (antagonized), unaffected, or completely changed by the binding of the reaction product. This will depend on the precise binding mode and the particular binding site the reaction product occupies on the target

Functional sites (such as protein-protein interaction or catalytic sites) on proteins often are more prone to bind molecules than are, other more neutral surface areas on a protein. In addition, these functional sites normally contain, a smaller region that seems to be primarily responsible for the binding energy: the so-called, hot-spot regions (Wells, et al. (1993) RECENT, PROG. HORMONE RES,. 48 : 253-262). This phenomenon facilitates selection for molecules affecting the biological function of a certain target

The linkage between the template molecule and reaction product allows rapid identification of binding molecules using various selection strategies. This invention broadly permits identifying binding molecules for any known target molecule. In addition, novel unknown targets can be discovered by isolating binding molecules against unknown antigens (epitopes) and using these binding molecules for

identification and validation. In another preferred embodiment, the target molecule is designed to mimic a transition state of a chemical reaction; one or more reaction products resulting from the selection may stabilize the transition state and catalyze the chemical reaction.

The upper limit for the strength of the stringency conditions is the disintegration of the complex comprising the displayed molecule and the encoding region. Screening conditions are known to one of ordinary skill in the art.

Complexes having predetermined desirable characteristics can be partitioned away from the rest of the library while still attached to a nucleic acid identifier tag by various methods known to one of ordinary skill in the art. In one embodiment of the invention the desirable products are partitioned away from the entire library without chemical degradation of the attached nucleic acid such that the identifier nucleic acids are amplifiable. The part of the identifier comprising the tags may then be amplified, either still attached to the desirable chemical compound or after separation from the desirable chemical compound.

Library members that bind a target molecule can be released by denaturation, acid, or chaotropic salts. Alternatively, elution conditions can be more specific to reduce background or to select for a desired specificity. Elution can be accomplished using proteolysis to cleave a linker between the target molecule and the immobilizing surface or between the reaction product and the template. Also, elution can be accomplished by competition with a known competitive ligand for the target molecule. Alternatively, a PCR reaction can be performed directly in the presence of the washed target molecules at the end of the selection procedure. Thus, the binding molecules need not be elutable from the target to be selectable since only the template is needed for further amplification or cloning, not the reaction product itself. Indeed, some target molecules bind the most avid ligands so tightly that elution would be difficult.

In a certain embodiment, the desirable molecule acts on the target without any interaction between the coding sequences attached to the desirable display compound and the target. In one embodiment, the desirable chemical compounds bind to the target followed by a partition of the complex from unbound products by a number of methods. The methods include plastic binding, nitrocellulose filter

binding, column chromatography, filtration, affinity chromatography, centrifugation, and other well known methods for immobilizing targets.

Briefly, the library is subjected to the partitioning step, which may include contact between the library and a column onto which the target is bound. All identifier sequences which do not encode for a reaction product having an activity towards the target will pass through the column. Additional undesirable chemical entities (e.g., entities which cross-react with other targets) can be removed by counter-selection methods. Desirable complexes are bound to the column and can be eluted by changing the conditions of the column (e.g., salt, etc.) or the identifier sequence associated with the desirable chemical compound can be cleaved off and eluted directly.

In a certain embodiment, the basic steps involve mixing the library of complexes with the immobilized target of interest. The target can be attached to a column matrix or microtitre wells with direct immobilization or by means of antibody binding or other high-affinity interactions. In another embodiment, the target and displayed molecules interact without immobilisation of the target. Displayed molecules that bind to the target will be retained on this surface, while nonbinding displayed molecules will be removed during a single or a series of wash steps. The identifiers of complexes bound to the target can then be separated by cleaving the physical connection to the synthetic molecule. It can be considered advantageously to perform a chromatography step after of (or) instead of the washing step. After the cleavage of the physical link between the synthetic molecule and the identifier, the identifier can be recovered from the media and optionally amplified before the decoding step.

In traditional elution protocols, false positives due to suboptimal binding and washing conditions are difficult to circumvent and may require elaborate adjustments of experimental conditions. However, an enrichment of more than 100 to 1000 is rarely obtained. The selection process used in example 7 herein alleviates the problem with false positive being obtained because the non-specific binding complexes to a large extent remain in the reaction chamber. The experiments reported herein suggest that an enrichment of more than 107 can be obtained.

Additionally, chemical compounds which react with a target can be separated from those products that do not react with the target. In one example, a chemical compound which covalently attaches to the target (such as a suicide inhibitor) can be washed under very stringent conditions. The resulting complex can then be treated with proteinase, DNAse or other suitable reagents to cleave a linker and liberate the nucleic acids which are associated with the desirable chemical compound. The liberated nucleic acids can be amplified.

In another example, the predetermined desirable characteristic of the desirable product is the ability of the product to transfer a chemical group (such as acyl transfer) to the target and thereby inactivate the target. One could have a product library where all of the products have a thioester chemical group, or similar activated chemical group. Upon contact with the target, the desirable products will transfer the chemical group to the target concomitantly changing the desirable product from a thioester to a thiol. Therefore, a partitioning method which would identify products that are now thiols (rather than thioesters) will enable the selection of the desirable products and amplification of the nucleic acid associated therewith.

There are other partitioning and screening processes which are compatible with this invention that are known to one of ordinary skill in the art. In one embodiment, the products can be fractionated by a number of common methods and then each fraction is then assayed for activity. The fractionization methods can include size, pH, hydrophobicity, etc.

To select for a molecule that binds a protein expressible on a cell surface, such as an ion channel or a transmembrane receptor, the cells themselves can be used as the selection agent. The library preferably is first exposed to cells not expressing the target molecule on their surfaces to remove library members that bind specifically or non specifically to other cell surface epitopes. Alternatively, cells lacking the target molecule are present in large excess in the selection process and separable (by fluorescence-activated cell sorting (FACS), for example) from cells bearing the target molecule. In either method, cells bearing the target molecule then are used to isolate library members bearing the target molecule (e.g., by sedimenting the cells or. by FACS sorting). For example, a recombinant DNA encoding the target molecule can be introduced into a cell line; library members that bind the transformed cells but not the untransformed cells are enriched for target molecule

binders. This approach is also called subtraction, selection and has been used for phage display on antibody libraries (Hoogenboom et al. (1998) IMMUNOTECH 4 : 20).

A selection procedure can also involve selection for binding to cell surface receptors that are internalized so that the. receptor together with the selected binding molecule passes into the cytoplasm, nucleus, or other cellular compartment, such as the Golgi or lysosomes. Depending on the dissociation rate constant for specific selected binding molecules, these molecules may localize primarily within the intracellular compartments. Internalized library members can be distinguished from molecules attached to the cell surface by washing the cells, preferably with a denaturant. More preferably, standard subcellular fractionation techniques are used to isolate the selected library members in a desired subcellular compartment.

An alternative selection protocol also includes a known, weak ligand affixed to each member of the library. The known ligand guides the selection by interacting with a defined part of the target molecule and focuses the selection on molecules that bind to the same region, providing a cooperative effect. This can be particularly useful for increasing the affinity of a ligand with a desired biological function but with too low a potency.

Other methods for selection or partitioning are also available for use with the present invention. These include, for example: immunoprecipitation (direct or indirect) where the target molecule is captured together with library members; mobility shift assays in agarose or polyacrylamide gels, where the selected library members migrate with the target molecule in a gel; cesium chloride gradient centrifugation to isolate the target molecule with library members; mass spectroscopy to identify target molecules labeled with library members. In general, any method where the library member/target molecule complex can be separated from library members not bound to the target is useful.

The selection process is well suited for optimizations, where the selection steps are made in series, starting with the selection of binding molecules and ending with an optimized binding molecule. The procedures in each step can be automated using various robotic systems.

Thus, the invention permits supplying a suitable library and target molecule to a fully automatic system which finally generates an optimized binding molecule. Under ideal conditions, this process should run without any requirement for external work outside the robotic system during the entire procedure.

The selection methods of the present invention can be combined with secondary selection or screening identify reaction products capable of modifying target molecule function upon binding., Thus, the methods, described herein can be employed to isolate or produce binding molecules that bind to and modify the function of any protein or, nucleic acid.

For example, nucleic acid-templated chemistry can be used to identify, isolate, or produce binding molecules (1) affecting catalytic activity of target enzymes by inhibiting catalysis or, modifying substrate binding ; (2) affecting the functionality of protein receptors, by inhibiting binding to receptors. or by modifying the specificity of binding to receptors; (3) affecting the formation of proteinmultimers by disrupting the quaternary structure of proteinsubunits ; or (4) modifying transport properties of a protein by disrupting transport of small molecules or ions.

Functional assays can be included in the selection process. For example,, after selecting for binding activity, selected library members can be directly tested for a desired functional effect, such as an effect on cell signaling. This can, for example, be performed via FACS methodologies..

The binding molecules of the invention can be selected for other properties in addition to binding. For example, to select for stability of binding interactions in a desired working environment. If stability in the presence of a certain protease is desired, that protease can be part of the buffer medium used during selection. Similarly, the selection can be performed in serum or cell extracts or in any type of medium, aqueous or organic. Conditions that disrupt or degrade the template should however be avoided to allow subsequent amplification.

Selections for other desired properties, such as catalytic or other functional activities, can also be performed. Generally, the selection should be designed such that library members with the desired activity are isolatable on that basis from other library members. For example, library members can be screened for the ability to

fold or otherwise significantly change conformation in the presence of a target molecule, such as a metal ion, or under particular pH or salinity conditions. The folded library members can be isolated by performing non-denaturing gel electrophoresis under the conditions of interest. The folded library members migrate to a different position in the gel and can subsequently be extracted from the gel and isolated.

Selection for catalytic activity may be performed by affinity selections on transition-state analog affinity columns (Baca et al. (1997) PROC. NATL. ACAD. Sci. USA 94 (19): 10063-8) or by function-based selection schemes (Pedersen et al. (1998) PROC. NATL. ACAD. Sci. USA 95 (18) : 10523-8).

Similarly, reaction products thatfluoresce in the presence of specific ligands may be selected by FACS based sorting of translated polymers linked through their DNA templates to beads. Those beads that fluoresce in the presence, but not in the absence, of the target ligand are' isolated and, characterized. Useful beads with a homogenous population of nucleic acid- templates-on any bead can be prepared using, thesplit-ppol synthesis technique on the bead, such that each bead is exposed to only a single nucleotide sequence. Alternatively, a different asti- " template (each complementary to only a single, different template) can by synthesized on beads using a split-pool'technique, and then can anneal to capture a solution-phase library.

Biotin-terminated biopolymers can be selected for the actual catalysis of bond-. breaking reactions by passing these biopolymers over a resin linked through a substrate to avidin. Those biopolymers that catalyzesubstrate cleavage self-elute from a column charged with this resin. Similarly, biotin-terminated biopolymers can be selected for the catalysis of bond-forming reactions. One substrate is linked to resin and the second substrate is linked to avidin. Biopolymers that catalyze bond formation between the substrates are selected by their ability to react the substrates together, resulting in attachment of the biopolymer to the resin.

Library members can also be selected for their catalytic effects on synthesis of a polymer to which the template is or becomes attached. For example, the library member may influence the selection of monomer units to be polymerized as well as how the polymerization reaction takes place (e. g., stereochemistry, tacticity,

activity). The synthesized polymers can be selected for specific properties, such as, molecular weight, density, hydrophobicity, tacticity, stereoselectivity, using standard techniques, such as, electrophoresis, gel filtration, centrifugal sedimentation, or partitioning into solvents of different hydrophobicities. The attached template that directed the synthesis of the polymer can then be identified.

Library members that catalyze virtually any reaction causing bond formation between two substrate molecules or resulting in bond breakage into two product molecules can be selected. To select for bond forming catalysts (for example, hetero Diels-Alder, Heck coupling, aldol reaction, or olefin metathesis catalysts), library members are covalently linked to one substrate through their 5'. amino or thiol termini. The other substrate of the reaction is synthesized as a derivative linked to biotin. When dilute solutions of library-substrate conjugate are combined with the substrate-biotin conjugate, those library members that catalyze bond formation cause the biotin group to become covalently attached to themselves. Active bond forming catalysts can then be separated from inactive library members by capturing the former with immobilized streptavidin and washing away inactive library members. In an analogous manner, library members that catalyze bond cleavage reactions such as retro-aldol reactions, amide hydrolysis, elimination reactions, or olefin dihydroxylation followed by periodate cleavage can be selected. In this case, library members are covalently linked to biotinylated substrates such that the bond breakage reaction causes the disconnection of the biotin moiety from the library members. Upon incubation under reaction conditions, active catalysts, but not inactive library members, induce the loss of their biotin groups.'Streptavidin-linked beads can then be used to capture inactive polymers, while active catalysts are able to be eluted from the beads. Related bond formation and bond cleavage selections have been used successfully in catalytic RNA and DNA evolution (Jaschke et al.(2000)CURR..OPIN. CHEM.BIOL. 4: 257-62) Although these selections do not explicitly select for multiple turnover catalysis, RNAs and DNAs selected in this manner have in general proven to be multiple turnover catalysts when separated from their substrate moieties (Jaschke etal. (2000) CURR. OPIN. CHEM.BIOL. 4: 257-62; Jaeger etal. (1999) PROC. NATL. ACAD.Sci. USA 96: 14712-7; Bartel etal. (1993) SCIENCE 261: 1411-8 ; Sen et aL (1998) CURR.OPIN. CHEM. BIOL. 2:680-7).

In addition to simply evolving active catalysts, the in vitro selections described above are used to evolve non-natural polymer libraries in powerful directions difficult to achieve using other catalyst discovery approaches. Substrate specificity among catalysts can be selected by selecting for active catalysts in the presence of the desired substrate and then selecting for inactive catalysts in the presence of one or more undesired substrates. If the desired and undesired substrates differ by their configuration at one or more stereocenters, enantioselective or diastereoselective catalysts can emerge from rounds of selection. Similarly, metal selectivity can be evolved by selecting for active catalysts in the presence of desired metals and selecting for inactive catalysts in the presence of undesired metals. Conversely, catalysts with broad substrate tolerance can be evolved by varying substrate structures between successive rounds of iteration.

Alternatively, following PCR amplification of DNA templates encoding selected synthetic molecules, additional rounds of translation, selection, and amplification can be conducted to enrich the library for high affinity binders. The stringency of the selection is gradually increased by increasing the salt concentration of the binding and washing buffers, decreasing the duration of binding, elevating the binding and washing temperatures, and increasing the concentration of washing additives such as template DNA or unrelated proteins.

Importantly, in vitro selections can also select for specificity in addition to binding affinity. Library screening methods for binding specificity typically require duplicating the entire screen for each target or non-target of interest. In contrast, selections for specificity can be performed in a single experiment by selecting for target binding as well as for the inability to bind one or more non-targets. Thus, the library can be pre-depleted by removing library members that bind to a non-target. Alternatively, or in addition, selection for binding to the target molecule can be performed in the presence of an excess of one or more non-targets. To maximize specificity, the non-target can be a homologous molecule. If the target molecule is a protein, appropriate non-target proteins include, for example, a generally promiscuous protein such as an albumin. If the binding assay is designed to target only a specific portion of a target molecule, the non-target can be a variation on the molecule in which that portion has been changed or removed.

Ultimately, a binding molecule identified using the present invention may be useful as a therapeutic and/or diagnostic agent. Once the selection is complete, the selected templates optionally can be amplified and sequenced. The selected reaction products, if present in sufficient quantity, can be separated from the templates, purified (e.g., by HPLC, column chromatography, or other chromatographic method), and further characterized.

Inherent in the present method is the selection of chemical entities on the basis of a desired function; this can be extended to the selection of small molecules with a desired function and specificity. Specificity can be required during the selection process by first extracting identifiers sequences of chemical compounds which are capable of interacting with a non-desired "target" (negative selection, or counter-selection), followed by positive selection with the desired target. As an example, inhibitors of fungal cytochrome P-450 are known to cross-react to some extent with mammalian cytochrome P-450 (resulting in serious side effects). Highly specific inhibitors of the fungal cytochrome could be selected from a library by first removing those products capable of interacting with the mammalian cytochrome, followed by retention of the remaining products which are capable of interacting with the fungal cytochrome.

Amplification of identifier oligonucleotides

PCR amplification methods are described in detail in U. S. Patent Nos. 4,683, 192, 4,683, 202,4, 800,159, and 4,965, 188, and at least in PCR Technology: Principles and Applications for DNA Amplification, H. Erlich, ed. , Stockton Press, New York (1989); and PCR Protocols: A Guide to Methods and Applications,Innis etal., eds. , Academic Press, San Diego,Calif. (1990). The contents of all the foregoing documents are incorporated herein by reference.

The identifier oligonucleotide can be amplified using PCR with primers generating two unique cut-sites. These cut-sites can be used for multimerization of the coding region by cloning into a suitable vector for sequencing. This approach will allow simultaneously sequencing of many encoding regions. Alternatively, the PCR product is directly cloned into a suitable vector using for example TA cloning. In still another approach the identity of the molecule is established by applying the PCR product to a suitable microarray.

It is preferred that the oligonucleotide parts of the bifunctional complexes of the libraries of the invention have a common terminal sequence which can serve as a primer for PCR, as is known in the art. Such a common terminal sequence can be incorporated as the terminal end of a tag added in the final cycle of the library synthesis, or it can be added following library synthesis, for example, using the enzymatic ligation methods disclosed herein.

In embodiments in which PCR is to be used to amplify the identifier oligonucleotides of selected bifunctional complexes, the identifier oligonucleotides preferably include PCR primer sequences. For example, a PCR primer sequence can be included in the display oligonucleotide and/or it can be included with the first tag oligonucleotide. The identifier oligonucleotide can also include a capping PCR primer sequence that follows the tag sequences. The capping sequence can be ligated to the identifier oligonucleotide following the final cycle of library synthesis or it can be included in the tag oligonucleotide of the final cycle. In cases in which the PCR primer sequences are included in a tag oligonucleotide, these tag oligonucleotides will be longer than the tag oligonucleotides added in the other cycles, because they will include both a tag sequence and a PCR primer sequence.

In cases in which the capping sequence is added after the addition of the final reactant and the final tag oligonucleotide, the synthesis of a library as set forth herein will include the step of ligating the capping sequence to the identifier oligonucleotide, such that the oligonucleotide portion of substantially all of the library members terminates in a sequence that includes a PCR primer sequence.

PCR primer sequences suitable for use in the libraries of the invention are known in the art; suitable primers and methods are set forth, for example, in Innis et al. , eds., PCR Protocols : A Guide to Methods and Applications, San Diego: Academic Press (1990), the contents of which are incorporated herein by reference in their entirety. Preferably, the capping sequence is added by ligation to the pooled fractions which are products of the final synthesis round. The capping sequence can be added using the enzymatic process used in the construction of the library.

As indicated above, the nucleotide sequence of the oligonucleotide tag as part of the methods of this invention, may be determined by the use of the polymerase chain reaction (PCR).

The nucleic acid sequence of an oligonucleotide tag can be determined by subjecting the oligonucleotide tag to a PCR reaction as follows. The appropriate sample is contacted with a PCR primer pair, each member of the pair having a preselected nucleotide sequence. The PCR primer pair is capable of initiating primer extension reactions by hybridizing to a PCR primer binding site on the identifier oligonucleotide tag. The PCR primer binding site is preferably designed into the identifier oligonucleotide tag. For example, a PCR primer binding site may be incorporated into the initial (display) oligonucleotide tag and the second PCR primer binding site may be in the final oligonucleotide tag. Alternatively, the second PCR primer binding site may be incorporated into the capping sequence as described herein. In preferred embodiments, the PCR primer binding site is at least about 5, 7,10, 13, 15, 17,20, 22, or 25 nucleotides in length.

The PCR reaction can be performed by mixing the PCR primer pair, preferably a predetermined amount thereof, with the identifier oligonucleotide, preferably a predetermined amount thereof, in a PCR buffer to form a PCR reaction admixture. The admixture isthermocycled for a number of cycles, which is typically predetermined, sufficient for the formation of a PCR reaction product. A sufficient amount of product is one that can be isolated in a sufficient amount to allow for DNA sequence determination.

PCR is typically carried out by thermocycling i.e. repeatedly increasing and decreasing the temperature of a PCR reaction admixture within a temperature range whose lower limit is about 30C to about 55C and whose upper limit is about 90C to about 100 C. The increasing and decreasing steps can be continuous, but is preferably phasic with time periods of relative temperature stability at each of temperatures favoring polynucleotide synthesis, denaturation and hybridization.

The PCR reaction can be performed using any suitable method. Generally it occurs in a buffered aqueous solution, i. e. a PCR buffer, preferably at a pH of 7-9. Preferably, a molar excess of the primer is present. A large molar excess is preferred to improve the efficiency of the process.

The PCR buffer also contains the deoxyribonucleotide triphosphates (polynucleotide synthesis substrates) dATP, dCTP, dGTP and dTTP and a polymerase, typically

thermostable, all in adequate amounts for primer extension (polynucleotide synthesis) reaction. The resultilig solution (PCR mixture) is-heated to about 90C-100 C for about 1 to 10 minutes, preferably from 1 to 4 minutes. After this heating period the solution is allowed to cool to 54C, which is preferable for primer hybridization.

The synthesis reaction may occur at a temperature ranging from room temperature up to a temperature above which the polymerase no longer functions efficiently. Suitable enzymes for elongating the primer sequences include, for example, E. coli DNA polymerase I, Taq DNA polymerase, Klenow fragmentof E. coli DNA polymeraseI, T4 DNA polymerase, other available DNA polymerases, reverse transcriptase, and other enzymes, including heat-stable enzymes, which will facilitate combination of the nucleotides in the proper manner to form the primer extension products which are complementary to each nucleic acid strand. Generally, the synthesis will be initiated at the 3'end of each primer and proceed in the 5'direction along the template strand, until synthesis terminates, producing molecules of different lengths. The newly synthesized DNA strand and its complementary strand form a double- stranded molecule which can be used in the succeeding steps of the analysis process.

Ultra High-Throughput Methods

Tags and/or identifiers may be analyzed by an ultra high throughput method, such as ultra high throughput sequencing as described herein below. Often following a screen or affinity assay using encoded molecules e.g. phage display, DNA display, mRNA display, or other types of tagged compounds, the results of screening may be analyzed by sampling a limited number of tags, e.g. 1-100 tags. Tags may be analyzed by cloning individual tags e.g. by cloning in E.coli followed by preparation of plasmids or “colony PCR” and then sequencing using any method known in the art. However, it is often desirable to analyse a significantly larger number of tags to obtain more information from the screening which makes these traditional methods of cloning and sequencing cumbersome. For example, a single type of sequence corresponding to a specific combination of codons may dominate a small tag sample e.g. 40 of 100 tags may correspond to a single codon combination and the remaining tags may be different. If instead 1000 or 10000 tags are analysed it is expected that about 400 and 4000 sequences respectively correspond to the tag observed 40 of 100 times in the small sample. However the remaining 600 and 6000 sequences respectively may reveal several sequences that are observed more than

once thus indicating that they have been preferentially enriched during the screening. Thus a potential wealth of information exists which is very cumbersome to access using traditional methods, e.g. e.g. by cloning in E.coli followed by preparation of plasmids or "colony PCR" and then sequencing. Several methods can be applied to analyze tags in an ultra high-throughput fashion. For example identifiers may be analyzed by an ultra high-throughput method similar to that described in patent WO0120039 and Margulies M et al (Genome sequencing in microfabricated high-density picolitre reactors, Nature 2005). This method involves capture of individual PCR-derived fragments on their own beads and, within the droplets of an emulsion, clonally amplifying the individual fragment. Unlike in current sequencing technology, this approach does not require subcloning in bacteria or the handling of individual clones; the templates are handled in bulk within the emulsions. Sequencing can be done by synthesis simultaneously in open wells of a fibre-optic slide using a modified pyrosequencing protocol that is designed to take advantage of the small scale of the wells. The fibreoptic slides are manufactured by slicing of a fibre-optic block that is obtained by repeated drawing and fusing of optic fibres. At each iteration, the diameters of the individual fibres decrease as they are hexagonally packed into bundles of increasing cross-sectional sizes. Each fibre-optic core is 44 μm in diameter and surrounded by 2–3 μm of cladding; etching of each core creates reaction wells approximately 55 μm in depth with a centre-to-centre distance of 50 μm, resulting in a calculated well size of 75 pl (picoliters). The slide, containing approximately 1.6 million wells, is loaded with beads and mounted in a flow chamber designed to create a 300-mm high channel, above the well openings, through which the sequencing reagents flow The unetched base of the slide is in optical contact with a second fibre optic imaging bundle bonded to a charge-coupled device (CCD) sensor, allowing the capture of emitted photons from the bottom of each individual well. The combination of picolitre-sized wells, enzyme loading uniformity allowed by the small beads and enhanced solid support chemistry enables a method that extends the useful read length of sequencing-by-synthesis to more than 100 bases.

Identifiers may also be analyzed by an ultra high-throughput method similar to that described in WO/2005/093094. This method relates to "high-density fingerprinting", in which a panel of nucleic acid probes is annealed to nucleic acid information is desired, e.g. an identifier, with determination of the presence or absence of sequence complementary to a panel of probes, thus providing sequence information. The method involves hybridization of a panel of probes, each probe

comprising one or more oligonucleotide molecules, in sequential steps determining for each probe if it hybridizes to the template or not, thus forming the "hybridization fingerprint" of the target. Preferably, the panel of probes and the length of the template strand are adjusted to ensure dense coverage of any given template strand with indicative probes' (probes which hybridize exactly once to the template strand). Probes may be 1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29, or 30 nucleotides long. Probes may contain any natural or unnatural nucleotide or analog. The obtained hybridization spectrum can then be compared with a reference database containing all expected identifier sequences. Before probing, identifiers or derived products may be immobilized in an array format. Then identifiers may be amplified e.g. using rolling-circle amplification or a related method. Thus individual identifier sequences are placed apart and amplified avoiding the need for traditional cumbersome cloning e.g. in e.coli.

Identifiers may also be analyzed by an ultra high-throughput method similar to that described in WO/2001/057248. By this method identifiers or amplified or modified identifiers may be immobilized in an array format. Primers may be annealed to the identifiers and the sequence of the identifiers may be determined by sequencing. Seqeuncing in an array format can be done by various methods recognized by those skilled in the art. For example, incorporation of fluorescently-labeled, 3'-blocked nucleotides can be done in the presence of a DNA polymerase. Nucleotide may be any natural or unnatural nucleotide or any nucleotide analog. The polymerase incorporates a base complementary to the target polynucleotide, but is prevented from further addition by the 3'-blocking group. The label of the incorporated base can then be determined and the blocking group removed by chemical cleavage to allow further polymerisation to occur. The flourescent group can also be removed thus allowing detection of a new nucleotide incorporation at a specific array positionn. Prior to immobilization, a hairpin adaptor may be ligated to the identifier sequence such that a primer becomes covalently linked to the identifier.

The information carried by tags may be analyzed using a computer application, e.g. a word or text processing application, a spreadsheet application, Preferably, the tag information may be analyzed using a computer application which can translate the tag information into e.g. encoded structures. A computer application may preferably be used to analyze such encoded structures include quantitative and qualitative

structure-activity relationship (SAR) analyses e.g. such as analyzing and/or clustering structural fingerprints common to enriched encoded structures. A simple but efficient method is to look for tag combinations which have been enriched by the screening process.

It may be found that only specific reactants or dimers formed by reactants, e.g., dimers formed by the first and the second reactant or the first and the third reactant are enriched by a screening process. Such a result may indicate that the screening process has not been optimized and steps can be taken to improve the screening process. If a large number of molecules with e.g. same or very similar target affinity exist in a library of bifunctional complexes it may be difficult or impossible to optimize the screening process so that it can discriminate sufficiently between them. The tag analysis may then identify a common reactant combination shared by the tags whereas one reactant position may be “undefined” i.e. it is not possible to determine which reactant is preferred at this position, e.g. the “C” position in the following list of tag combinations, where identifiers are composed of three tags (A-B-C): A2-B17-C13, A1-B1-C2, A1-B1-C14, A1-B1-C23, A1-B1-C17, A5-B278-C11. In this case is preferable to obtain significantly more tag sequences as this may enable discrimination of different but similar reactant combinations. This can be achieved by using ultra high-throughput tag sequencing methods as described.

Following screening or analyses of identifiers the pool of identifers may be subjected to further methods which may aid analyses of the identifiers. Such methods may include partitioning the identifiers based on specific features of the identifiers such as a nueclotide sequence. For example a subset of identifiers may contain too many variants of a tag combination or it may contains too much noise, e.g. identifers which are deemed uninteresting. In such cases nested PCR may be used to amplify only identifiers which contain specific tags. The resulting amplification product may then be processed e.g. sequencing, optionally in an ultra high-thoughput fashion, to identify a common tag at an otherwise unresolved position. Alternatively, tag combinations may be enriched by partitioning single-stranded identifier oligonucleotides e.g. sequentially with anticodons corresponding to specific tags essentially performing an affinity selection / screening of the identifiers with or without encoded molecules. In this way it is possible to partition specific identifiers or identifier subsets.

Targets

The methods described herein may involve partitioning of molecules or binfunctional complexes according to their affinity for a target. Targets may be protein or non-protein as discussed elsewhere. In the case of protein targets a list of applicable targets may be obtained e.g. by accessing an public database such as a NCBI database (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Protein). In the case of human enzymes and receptors, targets may be retrieved from said database using e.g. "Human" and "Enzyme" or "Receptor" as query keywords. Moreover, a list of targets can be retrieved from the "Mode of Action" section of the Medtrack database (medtrack.com).

A target suitable for use with the methods described herein can be selected from the list consisting of:

1:) (2'-5')oligo(A) synthetase (EC 2.7.7.-), splice form 8-2 - human; (2:) [3-methyl-2-oxobutanoate dehydrogenase [lipoamide]] kinase,mitochondrial precursor (Branched-chain alpha-ketoaciddehydrogenase kinase) (BCKDHKIN) (BCKD-kinase); (3:) [Protein ADP-ribosylarginine] hydrolase (ADP-ribosylargininehydrolase) (ADP-ribose-L-arginine cleaving enzyme); (4:) 1,4-alpha-glucan branching enzyme; (5:) 11 beta-hydroxysteroid dehydrogenase type II; (6:) 11-beta-hydroxysteroid dehydrogenase 1 [Homo sapiens]; (7:) 130 kDa leucine-rich protein (LRP 130) (GP130) (Leucine-rich PPRmotif-containing protein); (8:) 130 kDa phosphatidylinositol 4,5-biphosphate-dependent ARF1GTPase-activating protein (PIP2-dependent ARF1 GAP)(ADP-ribosylation factor-directed GTPase-activating protein 1) (ARFGTPase-activating protein 1) (Development anddifferentiation-enhancing factor 1); (9:) 14-3-3 protein zeta/delta (Protein kinase C inhibitor protein 1)(KCIP-1); (10:) 15-hydroxyprostaglandin dehydrogenase [NAD+] (PGDH) (Prostaglandindehydrogenase 1); (11:) 17 beta hydroxysteroid dehydrogenase type 2; (12:) 17beta-hydroxysteroid dehydrogenase type 10/short chainL-3-hydroxyacyl-CoA dehydrogenase [Homo sapiens]; (13:) 17beta-hydroxysteroid dehydrogenase type 7 form 2 [Homo sapiens]; (14:) 1-acylglycerol-3-phosphate O-acyltransferase 1 [Homo sapiens]; (15:) 1-acylglycerol-3-phosphate O-acyltransferase 5 [Homo sapiens]; (16:) 1-aminocyclopropane-1-carboxylate synthase [Homo sapiens]; (17:) 1-phosphatidylinositol-4,5-bisphosphate phosphodiesterase gamma

2(Phosphoinositide phospholipase C) (PLC-gamma-2) (PhospholipaseC-gamma-2) (PLC-IV); (18:) 2,4-dienoyl CoA reductase 1 precursor [Homo sapiens]; (19:) 2,4-dienoyl-CoA reductase, mitochondrial precursor (2,4-dienoyl-CoAreductase [NADPH]) (4-enoyl-CoA reductase [NADPH]); (20:) 2',5'-oligoadenylate synthetase 1 isoform 1 [Homo sapiens]; (21:) 2',5'-oligoadenylate synthetase 1 isoform 2 [Homo sapiens]; (22:) 2',5'-oligoadenylate synthetase 1 isoform 3 [Homo sapiens]; (23:) 2-5A-dependent ribonuclease (2-5A-dependent RNase) (Ribonuclease L)(RNase L) (Ribonuclease 4); (24:) 25-hydroxyvitamin D-1 alpha hydroxylase, mitochondrial precursor(Cytochrome P450 subfamily XXVIIB polypeptide 1) (Cytochrome p45027B1) (Calcidiol 1-monooxygenase) (25-OHD-1 alpha-hydroxylase)(25-hydroxyvitamin D(3) 1-alpha-hydroxylase) (VD3 1A hydroxylase)(P450C1 alpha) (P450VD1-alpha); (25:) 25-hydroxyvitamin D-1-alpha-hydroxylase [Homo sapiens]; (26:) 2'-5'oligoadenylate synthetase 3 [Homo sapiens]; (27:) 2'-5'-oligoadenylate synthetase-like isoform a [Homo sapiens]; (28:) 2'-5'-oligoadenylate synthetase-like isoform b [Homo sapiens]; (29:) 26S proteasome non-ATPase regulatory subunit 2 (26S proteasomeregulatory subunit RPN1) (26S proteasome regulatory subunit S2)(26S proteasome subunit p97) (Tumor necrosis factor type 1receptor-associated protein 2) (55.11 protein); (30:) 26S proteasome non-ATPase regulatory subunit 7 (26S proteasomeregulatory subunit rpn8) (26S proteasome regulatory subunit S12)(Proteasome subunit p40) (Mov34 protein homolog); (31:) 2-acylglycerol O-acyltransferase 2 (MonoacylglycerolO-acyltransferase 2) (Acyl CoA:monoacylglycerol acyltransferase 2)(MGAT2) (hMGAT2) (Diacylglycerol acyltransferase 2-like protein 5)(Diacylglycerol O-acyltransferase candidate 5) (hDC5); (32:) 2-acylglycerol O-acyltransferase 3 (MonoacylglycerolO-acyltransferase 3) (Acyl CoA:monoacylglycerol acyltransferase 3)(MGAT3) (Diacylglycerol acyltransferase 2-like protein 7)(Diacylglycerol O-acyltransferase candidate 7) (hDC7); (33:) 2-amino-3-carboxymuconate-6-semialdehyde decarboxylase; (34:) 2-amino-3-ketobutyrate coenzyme A ligase, mitochondrial precursor(AKB ligase) (Glycine acetyltransferase); (35:) 2-amino-3-ketobutyrate-CoA ligase [Homo sapiens]; (36:) 2-aminoadipic 6-semialdehyde dehydrogenase [Homo sapiens]; (37:) 2-enoyl-CoA hydratase, 3-hydroxyacyl-CoA dehydrogenase,3-oxoacyl-CoA thiolase, TFE beta=trifunctional enzyme beta subunit{N-terminal} [human, liver, Peptide Mitochondrial Partial, 16 aa]; (38:) 2-hydroxyacyl-CoA lyase 1 [Homo sapiens]; (39:) 2-hydroxyacylsphingosine 1-beta-galactosyltransferase (EC 2.4.1.45)- human; (40:) 2-hydroxyphytanoyl-CoA lyase (2-HPCL); (41:) 2-hydroxyphytanoyl-CoA lyase [Homo sapiens]; (42:) 2-oxoglutarate

dehydrogenase E1 component, mitochondrial precursor(Alpha-ketoglutarate dehydrogenase); (43:) 2-oxoglutarate receptor 1 (Alpha-ketoglutarate receptor 1)(G-protein coupled receptor 80) (G-protein coupled receptor 99)(P2Y purinoceptor 15) (P2Y-like nucleotide receptor) (P2Y-likeGPCR); (44:) "3 beta-hydroxysteroid dehydrogenase/delta 5-->4-isomerase type I(3Beta-HSD I) (Trophoblast antigen FDO161G) [Includes:3-beta-hydroxy-delta(5)-steroid dehydrogenase (3-beta-hydroxy-5-enesteroid dehydrogenase) (Progesterone reductase); Steroiddelta-isomerase (Delta-5-3-ketosteroid isomerase)]."; (45:) "3 beta-hydroxysteroid dehydrogenase/delta 5-->4-isomerase type II(3Beta-HSD II) [Includes:) 3-beta-hydroxy-delta(5)-steroiddehydrogenase (3-beta-hydroxy-5-ene steroid dehydrogenase)(Progesterone reductase); Steroid delta-isomerase(Delta-5-3-ketosteroid isomerase)]."; (46:) 3' histone mRNA exonuclease 1 (3'-5' exonuclease ERI1) (Eri-1homolog) (Histone mRNA 3' end-specific exoribonuclease) (Protein3'hExo) (HEXO); (47:) 3'(2'),5'-bisphosphate nucleotidase 1 (Bisphosphate 3'-nucleotidase1) (PAP-inositol-1,4-phosphatase) (PIP); (48:) 3,2-trans-enoyl-CoA isomerase, mitochondrial precursor(Dodecenoyl-CoA isomerase) (Delta(3),delta(2)-enoyl-CoA isomerase)(D3,D2-enoyl-CoA isomerase); (49:) 3',5'-cyclic nucleotide phosphodiesterase (EC 3.1.4.17) 8B1 -human; (50:) 3-hydroxy-3-methylglutaryl coenzyme A reductase; (51:) "3-hydroxyacyl-CoA dehydrogenase; peroxisomal enoyl-CoA hydratase[Homo sapiens]."; (52:) 3-hydroxybutyrate dehydrogenase precursor [Homo sapiens]; (53:) 3-hydroxybutyrate dehydrogenase type 2 (R-beta-hydroxybutyratedehydrogenase) (Dehydrogenase/reductase SDR family member 6)(Oxidoreductase UCPA); (54:) 3-hydroxybutyrate dehydrogenase, type 2 [Homo sapiens]; (55:) 3-hydroxyisobutyrate dehydrogenase [Homo sapiens]; (56:) 3-hydroxymethyl-3-methylglutaryl-Coenzyme A lyase(hydroxymethylglutaricaciduria) [Homo sapiens]; (57:) 3-keto-steroid reductase (Estradiol 17-beta-dehydrogenase 7)(17-beta-HSD 7) (17-beta-hydroxysteroid dehydrogenase 7); (58:) 3-mercaptopyruvate sulfurtransferase [Homo sapiens]; (59:) 3-methylcrotonyl-CoA carboxylase alpha subunit [Homo sapiens]; (60:) 3-methylcrotonyl-CoA carboxylase biotin-containing subunit [Homosapiens]; (61:) 3-oxo-5 alpha-steroid 4-dehydrogenase 2 [Homo sapiens]; (62:) 3-oxo-5-beta-steroid 4-dehydrogenase (Delta(4)-3-ketosteroid5-beta-reductase) (Aldo-keto reductase family 1 member D1); (63:) 3-oxoacid CoA transferase 1 precursor [Homo sapiens]; (64:) 3-oxoacyl-[acyl-carrier-protein] synthase, mitochondrial precursor(Beta-ketoacyl synthase); (65:) 3'-phosphoadenosine 5'-phosphosulfate synthase 1 [Homo sapiens]; (66:) 3'phosphoadenosine 5'-phosphosulfate synthase 2b isoform [Homosapiens]; (67:)

40 kDa peptidyl-prolyl cis-trans isomerase (PPIase) (Rotamase)(Cyclophilin-40) (CYP-40) (Cyclophilin-related protein); (68:) 4a-carbinolamine dehydratase; (69:) 4-alpha-glucanotransferase (EC 2.4.1.25) / amylo-1, 6-glucosidase(EC 3.2.1.33) - human; (70:) 4-aminobutyrate aminotransferase precursor [Homo sapiens]; (71:) 4-trimethylaminobutyraldehyde dehydrogenase (TMABADH) (Aldehydedehydrogenase 9A1) (Aldehyde dehydrogenase E3 isozyme)(Gamma-aminobutyraldehyde dehydrogenase) (R-aminobutyraldehydedehydrogenase); (72:) 5' nucleotidase, ecto [Homo sapiens]; (73:) 5'(3')-deoxyribonucleotidase, cytosolic type (Cytosolic5',3'-pyrimidine nucleotidase) (Deoxy-5'-nucleotidase 1) (dNT-1); (74:) 5,10-methylenetetrahydrofolate reductase (NADPH) [Homo sapiens]; (75:) 5',3'-nucleotidase, cytosolic [Homo sapiens]; (76:) 5',3'-nucleotidase, mitochondrial precursor [Homo sapiens]; (77:) 52kD Ro/SSA autoantigen [Homo sapiens]; (78:) 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMPcyclohydrolase [Homo sapiens]; (79:) 5-aminolevulinate synthase, erythroid-specific, mitochondrialprecursor (5-aminolevulinic acid synthase) (Delta-aminolevulinatesynthase) (Delta-ALA synthetase) (ALAS-E); (80:) 5-aminolevulinate synthase, nonspecific, mitochondrial precursor(5-aminolevulinic acid synthase) (Delta-aminolevulinate synthase)(Delta-ALA synthetase) (ALAS-H); (81:) 5-beta steroid reductase [Homo sapiens]; (82:) 5-hydroxytryptamine 1A receptor (5-HT-1A) (Serotonin receptor 1A)(5-HT1A) (G-21); (83:) 5-hydroxytryptamine 1B receptor (5-HT-1B) (Serotonin receptor 1B)(5-HT1B) (5-HT-1D-beta) (Serotonin 1D beta receptor) (S12); (84:) 5-hydroxytryptamine 1D receptor (5-HT-1D) (Serotonin receptor 1D)(5-HT-1D-alpha); (85:) 5-hydroxytryptamine 1E receptor (5-HT-1E) (Serotonin receptor 1E)(5-HT1E) (S31); (86:) 5-hydroxytryptamine 1F receptor (5-HT-1F) (Serotonin receptor 1F); (87:) 5-hydroxytryptamine 2A receptor (5-HT-2A) (Serotonin receptor 2A)(5-HT-2); (88:) 5-hydroxytryptamine 2B receptor (5-HT-2B) (Serotonin receptor 2B); (89:) 5-hydroxytryptamine 2C receptor (5-HT-2C) (Serotonin receptor 2C)(5-HT2C) (5-HTR2C) (5HT-1C); (90:) 5-hydroxytryptamine 3 receptor precursor (5-HT-3) (Serotonin-gatedion channel receptor) (5-HT3R); (91:) 5-hydroxytryptamine 4 receptor (5-HT-4) (Serotonin receptor 4)(5-HT4); (92:) 5-hydroxytryptamine 5A receptor (5-HT-5A) (Serotonin receptor 5A)(5-HT-5); (93:) 5-hydroxytryptamine 6 receptor (5-HT-6) (Serotonin receptor 6); (94:) 5-hydroxytryptamine 7 receptor (5-HT-7) (Serotonin receptor 7)(5-HT-X) (5HT7); (95:) 5-methyltetrahydrofolate-homocysteine methyltransferase [Homosapiens]; (96:) 5'-methylthioadenosine phosphorylase [Homo sapiens]; (97:) 5'-nucleotidase, cytosolic II [Homo sapiens]; (98:) 5'-nucleotidase, cytosolic III isoform 1 [Homo sapiens]; (99:)

6-phosphofructo-2-kinase (EC 2.7.1.105) / fructose-2,6-bisphosphate 2-phosphatase (EC 3.1.3.46) - human; (100:) "6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 1(6PF-2-K/Fru-2,6-P2ASE liver isozyme) [Includes:6-phosphofructo-2-kinase ; Fructose-2,6-bisphosphatase]."; (101:) 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 2 isoform a[Homo sapiens]; (102:) 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 2 isoform b[Homo sapiens]; (103:) "6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 2(6PF-2-K/Fru-2,6-P2ASE heart-type isozyme) (PFK-2/FBPase-2)[Includes:) 6-phosphofructo-2-kinase ; Fructose-2,6-bisphosphatase]."; (104:) 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 4 [Homosapiens]; (105:) 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 4 spliceisoform 3 [Homo sapiens]; (106:) 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 4 spliceisoform 4 [Homo sapiens]; (107:) 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 4 spliceisoform 5 [Homo sapiens]; (108:) "6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 4(6PF-2-K/Fru-2,6-P2ASE testis-type isozyme) [Includes:6-phosphofructo-2-kinase ; Fructose-2,6-bisphosphatase]."; (109:) 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase-4 isoform 2[Homo sapiens]; (110:) 6-phosphofructokinase (EC 2.7.1.11), hepatic - human; (111:) 6-phosphofructokinase type C (Phosphofructokinase 1)(Phosphohexokinase) (Phosphofructo-1-kinase isozyme C) (PFK-C)(6-phosphofructokinase, platelet type); (112:) 6-phosphofructokinase, liver type (Phosphofructokinase 1)(Phosphohexokinase) (Phosphofructo-1-kinase isozyme B) (PFK-B); (113:) 6-phosphofructokinase, muscle type (Phosphofructokinase 1)(Phosphohexokinase) (Phosphofructo-1-kinase isozyme A) (PFK-A)(Phosphofructokinase-M); (114:) 6-phosphogluconolactonase (6PGL); (115:) 6-pyruvoyl tetrahydrobiopterin synthase (PTPS) (PTP synthase); (116:) 6-pyruvoyltetrahydropterin synthase [Homo sapiens]; (117:) 7,8-dihydro-8-oxoguanine triphosphatase (8-oxo-dGTPase) (Nucleosidediphosphate-linked moiety X motif 1) (Nudix motif 1); (118:) 72 kDa type IV collagenase precursor (72 kDa gelatinase) (Matrixmetalloproteinase-2) (MMP-2) (Gelatinase A) (TBE-1); (119:) 85 kDa calcium-independent phospholipase A2 (iPLA2) (Cal-PLA2)(Group VI phospholipase A2) (GVI PLA2); (120:) 8-hydroxyguanine-DNA glycosylase [Homo sapiens]; (121:) 8-oxo-7,8-dihydroguanosine triphophatase - human; (122:) 8-oxo-dGTPase [Homo sapiens]; (123:) 8-oxoguanine DNA glycosylase 1 [Homo sapiens]; (124:) 8-oxoguanine DNA glycosylase homolog 1 [Homo sapiens]; (125:) 8-oxoguanine DNA glycosylase isoform 1a [Homo sapiens]; (126:) 8-oxoguanine DNA glycosylase isoform 1b [Homo sapiens]; (127:) 8-oxoguanine DNA glycosylase

isoform 1c [Homo sapiens]; (128:) 8-oxoguanine DNA glycosylase isoform 2a [Homo sapiens]; (129:) 8-oxoguanine DNA glycosylase isoform 2b [Homo sapiens]; (130:) 8-oxoguanine DNA glycosylase isoform 2c [Homo sapiens]; (131:) 8-oxoguanine DNA glycosylase isoform 2d [Homo sapiens]; (132:) 8-oxoguanine DNA glycosylase isoform 2e [Homo sapiens]; (133:) 92-kDa type IV collagenase [Homo sapiens]; (134:) 9-cis-retinol specific dehydrogenase [Homo sapiens]; (135:) A Transferase [Homo sapiens]; (136:) A/G-specific adenine DNA glycosylase (MutY homolog) (hMYH); (137:) ACAD 10 [Homo sapiens]; (138:) Ac-CoA carboxylase; (139:) ACE2 [Homo sapiens]; (140:) ACE-related carboxypeptidase ACE2 [Homo sapiens]; (141:) Acetoacetyl-CoA synthetase [Homo sapiens]; (142:) Acetolactate synthase [Homo sapiens]; (143:) acetolactate synthase homolog; (144:) Acetylcholine receptor protein subunit alpha precursor; (145:) Acetylcholine receptor protein subunit beta precursor; (146:) Acetylcholine receptor protein subunit delta precursor; (147:) Acetylcholine receptor protein subunit epsilon precursor; (148:) Acetylcholine receptor protein subunit gamma precursor; (149:) Acetylcholinesterase collagenic tail peptide precursor (AChE Qsubunit) (Acetylcholinesterase-associated collagen); (150:) acetylcholinesterase collagen-like tail subunit [Homo sapiens]; (151:) acetylcholinesterase collagen-like tail subunit isoform I precursor[Homo sapiens]; (152:) acetylcholinesterase collagen-like tail subunit isoform II [Homosapiens]; (153:) acetylcholinesterase collagen-like tail subunit isoform III [Homosapiens]; (154:) acetylcholinesterase collagen-like tail subunit isoform IIIprecursor [Homo sapiens]; (155:) acetylcholinesterase collagen-like tail subunit isoform IV [Homosapiens]; (156:) acetylcholinesterase collagen-like tail subunit isoform IVprecursor [Homo sapiens]; (157:) acetylcholinesterase collagen-like tail subunit isoform V [Homosapiens]; (158:) acetylcholinesterase collagen-like tail subunit isoform V precursor[Homo sapiens]; (159:) acetylcholinesterase collagen-like tail subunit isoform VI [Homosapiens]; (160:) acetylcholinesterase collagen-like tail subunit isoform VII [Homosapiens]; (161:) acetylcholinesterase collagen-like tail subunit isoform VIII [Homosapiens]; (162:) acetylcholinesterase collagen-like tail subunit isoform VIIIprecursor [Homo sapiens]; (163:) acetylcholinesterase collagen-like tail subunit isoform VIIprecursor [Homo sapiens]; (164:) acetylcholinesterase collagen-like tail subunit isoform VIprecursor [Homo sapiens]; (165:) acetylcholinesterase isoform E4-E5 precursor [Homo sapiens]; (166:) acetyl-CoA carboxylase (EC 6.4.1.2) - human; (167:) Acetyl-CoA carboxylase 1 (ACC-alpha) [Includes:) Biotin carboxylase]; (168:) acetyl-CoA carboxylase 1 [Homo sapiens]; (169:) Acetyl-CoA carboxylase 2 (ACC-beta) [Includes:) Biotin carboxylase]; (170:) acetyl-CoA

carboxylase 2 [Homo sapiens]; (171:) Acetyl-CoA carboxylase 2 variant [Homo sapiens]; (172:) acetyl-CoA carboxylase alpha [Homo sapiens]; (173:) acetyl-CoA synthetase [Homo sapiens]; (174:) acetyl-Coenzyme A acetyltransferase 1 precursor [Homo sapiens]; (175:) acetyl-Coenzyme A acetyltransferase 2 [Homo sapiens]; (176:) acetyl-Coenzyme A acyltransferase 1 [Homo sapiens]; (177:) acetyl-Coenzyme A carboxylase alpha isoform 1 [Homo sapiens]; (178:) acetyl-Coenzyme A carboxylase alpha isoform 2 [Homo sapiens]; (179:) acetyl-Coenzyme A carboxylase alpha isoform 3 [Homo sapiens]; (180:) acetyl-Coenzyme A carboxylase alpha isoform 4 [Homo sapiens]; (181:) acetyl-Coenzyme A carboxylase beta [Homo sapiens]; (182:) Acetyl-coenzyme A synthetase 2-like, mitochondrial precursor(Acetate--CoA ligase 2) (Acetyl-CoA synthetase 2) (Acyl-CoAsynthetase short-chain family member 1); (183:) Acetyl-coenzyme A synthetase, cytoplasmic (Acetate--CoA ligase)(Acyl-activating enzyme) (Acetyl-CoA synthetase) (ACS) (AceCS)(Acyl-CoA synthetase short-chain family member 2); (184:) acid alpha-glucosidase preproprotein [Homo sapiens]; (185:) acid phosphatase 1 isoform b [Homo sapiens]; (186:) acid phosphatase 1 isoform c [Homo sapiens]; (187:) acid phosphatase 1 isoform d [Homo sapiens]; (188:) acid phosphatase 6, lysophosphatidic [Homo sapiens]; (189:) acid phosphatase; (190:) aconitase 2 precursor [Homo sapiens]; (191:) Aconitate hydratase, mitochondrial precursor (Citrate hydro-lyase)(Aconitase); (192:) acrosin precursor [Homo sapiens]; (193:) ACSBG2 protein [Homo sapiens]; (194:) ACSL1 protein [Homo sapiens]; (195:) ACSL3 protein [Homo sapiens]; (196:) ACSL6 protein [Homo sapiens]; (197:) ACSM1 protein [Homo sapiens]; (198:) ACSS2 protein [Homo sapiens]; (199:) activating transcription factor 2 [Homo sapiens]; (200:) activation of Sentrin/SUMO protein AOS1 [Homo sapiens]; (201:) activation-induced cytidine deaminase [Homo sapiens]; (202:) activin A receptor, type IC [Homo sapiens]; (203:) activin A receptor, type IIA precursor [Homo sapiens]; (204:) activin A type IB receptor isoform a precursor [Homo sapiens]; (205:) activin A type IB receptor isoform b precursor [Homo sapiens]; (206:) activin A type IB receptor isoform c precursor [Homo sapiens]; (207:) activin A type IIB receptor precursor [Homo sapiens]; (208:) Activin receptor type 1B precursor (ACTR-IB)(Serine/threonine-protein kinase receptor R2) (SKR2) (Activinreceptor-like kinase 4) (ALK-4); (209:) Activin receptor type 1C precursor (ACTR-IC) (Activin receptor-likekinase 7) (ALK-7); (210:) Activin receptor type 2A precursor (Activin receptor type IIA)(ACTR-IIA) (ACTRIIA); (211:) Activin receptor type 2B precursor (Activin receptor type IIB)(ACTR-IIB); (212:) Activin receptor type-1 precursor (Activin receptor type I)(ACTR-I) (Serine/threonine-protein

kinase receptor R1) (SKR1)(Activin receptor-like kinase 2) (ALK-2) (TGF-B superfamilyreceptor type I) (TSR-I); (213:) acyl coenzyme A:cholesterol acyltransferase [Homo sapiens]; (214:) acyl coenzyme A:monoacylglycerol acyltransferase 3 [Homo sapiens]; (215:) acylamino acid-releasing enzyme [Homo sapiens]; (216:) Acylamino-acid-releasing enzyme (AARE) (Acyl-peptide hydrolase)(APH) (Acylaminoacyl-peptidase) (Oxidized protein hydrolase) (OPH)(DNF15S2 protein); (217:) Acyl-CoA dehydrogenase family member 8, mitochondrial precursor(ACAD-8) (Isobutyryl-CoA dehydrogenase) (Activator-recruitedcofactor 42 kDa component) (ARC42); (218:) Acyl-CoA synthetase 3 [Homo sapiens]; (219:) acyl-CoA synthetase 4 [Homo sapiens]; (220:) Acyl-CoA synthetase bubblegum family member 2 [Homo sapiens]; (221:) acyl-CoA synthetase long-chain family member 1 [Homo sapiens]; (222:) acyl-CoA synthetase long-chain family member 1 isoform a [Homosapiens]; (223:) acyl-CoA synthetase long-chain family member 1 isoform c [Homosapiens]; (224:) acyl-CoA synthetase long-chain family member 3 [Homo sapiens]; (225:) Acyl-CoA synthetase long-chain family member 4 [Homo sapiens]; (226:) acyl-CoA synthetase long-chain family member 4 isoform 1 [Homosapiens]; (227:) acyl-CoA synthetase long-chain family member 4 isoform 2 [Homosapiens]; (228:) Acyl-CoA synthetase long-chain family member 5 [Homo sapiens]; (229:) acyl-CoA synthetase long-chain family member 5 isoform a [Homosapiens]; (230:) acyl-CoA synthetase long-chain family member 5 isoform b [Homosapiens]; (231:) acyl-CoA synthetase long-chain family member 6 isoform a [Homosapiens]; (232:) acyl-CoA synthetase long-chain family member 6 isoform b [Homosapiens]; (233:) acyl-CoA synthetase long-chain family member 6 isoform d [Homosapiens]; (234:) acyl-CoA synthetase long-chain family member 6 isoform e [Homosapiens]; (235:) Acyl-CoA synthetase medium-chain family member 3 [Homo sapiens]; (236:) Acyl-CoA synthetase short-chain family member 1 [Homo sapiens]; (237:) Acyl-CoA synthetase short-chain family member 2 [Homo sapiens]; (238:) acyl-CoA synthetase short-chain family member 2 isoform 1 [Homosapiens]; (239:) acyl-CoA synthetase short-chain family member 2 isoform 2 [Homosapiens]; (240:) acyl-CoA synthetase-like protein [Homo sapiens]; (241:) Acyl-CoA wax alcohol acyltransferase 1 (Long-chain-alcoholO-fatty-acyltransferase 1) (Diacylglycerol O-acyltransferase 2-likeprotein 3) (Diacyl-glycerol acyltransferase 2); (242:) Acyl-CoA wax alcohol acyltransferase 2 (Long-chain-alcoholO-fatty-acyltransferase 2) (Wax synthase) (hWS) (MultifunctionalO-acyltransferase) (Diacylglycerol O-acyltransferase 2-like protein4) (Diacylglycerol O-acyltransferase candidate 4) (hDC4); (243:) acyl-Coenzyme A dehydrogenase family, member 10

[Homo sapiens]; (244:) Acyl-Coenzyme A dehydrogenase family, member 11 [Homo sapiens]; (245:) acyl-Coenzyme A dehydrogenase family, member 8 [Homo sapiens]; (246:) acyl-Coenzyme A dehydrogenase, C-2 to C-3 short chain precursor[Homo sapiens]; (247:) acyl-Coenzyme A dehydrogenase, C-4 to C-12 straight chain [Homosapiens]; (248:) acyl-Coenzyme A dehydrogenase, long chain precursor [Homo sapiens]; (249:) acyl-Coenzyme A dehydrogenase, short/branched chain precursor [Homosapiens]; (250:) acyl-Coenzyme A oxidase 2, branched chain [Homo sapiens]; (251:) acyl-Coenzyme A oxidase 3, pristanoyl [Homo sapiens]; (252:) acyl-Coenzyme A oxidase isoform a [Homo sapiens]; (253:) acyl-Coenzyme A oxidase isoform b [Homo sapiens]; (254:) Acyl-coenzyme A thioesterase 8 (Acyl-CoA thioesterase 8)(Peroxisomal acyl-coenzyme A thioester hydrolase 1) (PTE-1)(Peroxisomal long-chain acyl-coA thioesterase 1)(HIV-Nef-associated acyl coA thioesterase) (Thioesterase II) (hTE)(hACTEIII) (hACTE-III) (PTE-2); (255:) acyl-malonyl condensing enzyme [Homo sapiens]; (256:) acyl-malonyl condensing enzyme 1 [Homo sapiens]; (257:) acyloxyacyl hydrolase precursor [Homo sapiens]; (258:) acyloxyacyl hydrolase; (259:) ADAM 10 precursor (A disintegrin and metalloproteinase domain 10)(Mammalian disintegrin-metalloprotease) (Kuzbanian protein homolog)(CDw156c antigen); (260:) ADAM 17 precursor (A disintegrin and metalloproteinase domain 17)(TNF-alpha-converting enzyme) (TNF-alpha convertase) (Snakevenom-like protease) (CD156b antigen); (261:) ADAM metallopeptidase domain 10 [Homo sapiens]; (262:) ADAM metallopeptidase domain 12 isoform 1 preproprotein [Homosapiens]; (263:) ADAM metallopeptidase domain 12 isoform 2 preproprotein [Homosapiens]; (264:) ADAM metallopeptidase domain 17 preproprotein [Homo sapiens]; (265:) ADAM metallopeptidase domain 19 isoform 1 preproprotein [Homosapiens]; (266:) ADAM metallopeptidase domain 19 isoform 2 preproprotein [Homosapiens]; (267:) ADAM metallopeptidase domain 33 isoform alpha preproprotein [Homosapiens]; (268:) ADAM metallopeptidase domain 33 isoform beta preproprotein [Homosapiens]; (269:) ADAM metallopeptidase with thrombospondin type 1 motif, 12preproprotein [Homo sapiens]; (270:) ADAM metallopeptidase with thrombospondin type 1 motif, 13 isoform1 preproprotein [Homo sapiens]; (271:) ADAM metallopeptidase with thrombospondin type 1 motif, 13 isoform2 preproprotein [Homo sapiens]; (272:) ADAM metallopeptidase with thrombospondin type 1 motif, 13 isoform3 preproprotein [Homo sapiens]; (273:) ADAM metallopeptidase with thrombospondin type 1 motif, 1preproprotein [Homo sapiens]; (274:) ADAM metallopeptidase with thrombospondin type 1 motif, 2 isoform 1preproprotein [Homo sapiens]; (275:) ADAM metallopeptidase with

thrombospondin type 1 motif, 2 isoform 2[Homo sapiens]; (276:) ADAM metallopeptidase with thrombospondin type 1 motif, 3proprotein [Homo sapiens]; (277:) ADAM metallopeptidase with thrombospondin type 1 motif, 4preproprotein [Homo sapiens]; (278:) ADAM metallopeptidase with thrombospondin type 1 motif, 5preproprotein [Homo sapiens]; (279:) ADAM metallopeptidase with thrombospondin type 1 motif, 8preproprotein [Homo sapiens]; (280:) ADAM10 [Homo sapiens]; (281:) ADAMTS-13 precursor (A disintegrin and metalloproteinase withthrombospondin motifs 13) (ADAM-TS 13) (ADAM-TS13) (von Willebrandfactor-cleaving protease) (vWF-cleaving protease) (vWF-CP); (282:) ADAMTS-14 precursor (A disintegrin and metalloproteinase withthrombospondin motifs 14) (ADAM-TS 14) (ADAM-TS14); (283:) ADAMTS-2 precursor (A disintegrin and metalloproteinase withthrombospondin motifs 2) (ADAM-TS 2) (ADAM-TS2) (Procollagen I/IIamino propeptide-processing enzyme) (Procollagen I N-proteinase)(PC I-NP) (Procollagen N-endopeptidase) (pNPI); (284:) ADAMTS-3 precursor (A disintegrin and metalloproteinase withthrombospondin motifs 3) (ADAM-TS 3) (ADAM-TS3) (Procollagen IIamino propeptide-processing enzyme) (Procollagen II N-proteinase)(PC II-NP); (285:) adaptor-related protein complex 2, alpha 1 subunit isoform 1 [Homosapiens]; (286:) adaptor-related protein complex 2, alpha 1 subunit isoform 2 [Homosapiens]; (287:) Adenine phosphoribosyltransferase (APRT); (288:) adenine phosphoribosyltransferase isoform a [Homo sapiens]; (289:) adenine phosphoribosyltransferase isoform b [Homo sapiens]; (290:) Adenosine A1 receptor; (291:) Adenosine A2a receptor; (292:) Adenosine A2b receptor; (293:) Adenosine A3 receptor; (294:) adenosine deaminase [Homo sapiens]; (295:) adenosine deaminase variant [Homo sapiens]; (296:) adenosine deaminase, RNA-specific isoform a [Homo sapiens]; (297:) adenosine deaminase, RNA-specific isoform b [Homo sapiens]; (298:) adenosine deaminase, RNA-specific isoform c [Homo sapiens]; (299:) adenosine deaminase, RNA-specific isoform d [Homo sapiens]; (300:) adenosine kinase isoform a [Homo sapiens]; (301:) adenosine kinase isoform b [Homo sapiens]; (302:) adenosine monophosphate deaminase 1 (isoform M) [Homo sapiens]; (303:) adenylate cyclase (EC 4.6.1.1) - human (fragment); (304:) adenylate cyclase 2 [Homo sapiens]; (305:) adenylate cyclase 3 [Homo sapiens]; (306:) adenylate cyclase 5 [Homo sapiens]; (307:) adenylate cyclase 6 isoform a [Homo sapiens]; (308:) adenylate cyclase 6 isoform b [Homo sapiens]; (309:) adenylate cyclase 7 [Homo sapiens]; (310:) adenylate cyclase 8 [Homo sapiens]; (311:) adenylate cyclase 9 [Homo sapiens]; (312:) adenylate cyclase activating polypeptide 1 (pituitary) receptortype I precursor [Homo sapiens];

(313:) Adenylate cyclase type 1 (Adenylate cyclase type I) (ATPpyrophosphate-lyase 1) (Ca(2+)/calmodulin-activated adenylylcyclase); (314:) Adenylate cyclase type 2 (Adenylate cyclase type II) (ATPpyrophosphate-lyase 2) (Adenylyl cyclase 2); (315:) Adenylate cyclase type 3 (Adenylate cyclase type III) (Adenylatecyclase, olfactive type) (ATP pyrophosphate-lyase 3) (Adenylylcyclase 3) (AC-III) (AC3); (316:) Adenylate cyclase type 4 (Adenylate cyclase type IV) (ATPpyrophosphate-lyase 4) (Adenylyl cyclase 4); (317:) Adenylate cyclase type 5 (Adenylate cyclase type V) (ATPpyrophosphate-lyase 5) (Adenylyl cyclase 5); (318:) Adenylate cyclase type 6 (Adenylate cyclase type VI) (ATPpyrophosphate-lyase 6) (Ca(2+)-inhibitable adenylyl cyclase); (319:) Adenylate cyclase type 8 (Adenylate cyclase type VIII) (ATPpyrophosphate-lyase 8) (Ca(2+)/calmodulin-activated adenylylcyclase); (320:) Adenylate cyclase type 9 (Adenylate cyclase type IX) (ATPpyrophosphate-lyase 9) (Adenylyl cyclase 9); (321:) adenylate kinase 1 [Homo sapiens]; (322:) adenylate kinase 2 isoform a [Homo sapiens]; (323:) adenylate kinase 2 isoform b [Homo sapiens]; (324:) Adenylate kinase isoenzyme 1 (ATP-AMP transphosphorylase) (AK1)(Myokinase); (325:) Adenylate kinase isoenzyme 2, mitochondrial (ATP-AMPtransphosphorylase); (326:) Adenylate kinase isoenzyme 5 (ATP-AMP transphosphorylase); (327:) Adenylate kinase isoenzyme 6 (ATP-AMP transphosphorylase 6); (328:) Adenylosuccinate lyase (Adenylosuccinase) (ASL) (ASASE); (329:) adenylosuccinate lyase [Homo sapiens]; (330:) adenylosuccinate synthase [Homo sapiens]; (331:) adhesion regulating molecule 1 precursor [Homo sapiens]; (332:) adiponectin precursor [Homo sapiens]; (333:) Adiponectin receptor protein 1 (Progestin and adipoQ receptorfamily member I); (334:) Adiponectin receptor protein 2 (Progestin and adipoQ receptorfamily member II); (335:) "Adiponutrin (iPLA2-epsilon) (Calcium-independent phospholipaseA2-epsilon) (Patatin-like phospholipase domain-containing protein3) [Includes:) Triacylglycerol lipase ; AcylglycerolO-acyltransferase]."; (336:) ADP-ribosyl cyclase 1 (Cyclic ADP-ribose hydrolase 1) (cADPrhydrolase 1) (Lymphocyte differentiation antigen CD38) (T10) (Acutelymphoblastic leukemia cells antigen CD38); (337:) ADP-ribosylarginine hydrolase [Homo sapiens]; (338:) ADP-ribosylation factor binding protein 2 [Homo sapiens]; (339:) ADP-ribosyltransferase 5 precursor [Homo sapiens]; (340:) adrenal gland protein AD-004 [Homo sapiens]; (341:) Adrenocorticotropic hormone receptor (ACTH receptor) (ACTH-R)(Melanocortin receptor 2) (MC2-R) (Adrenocorticotropin receptor); (342:) Adrenomedullin receptor (AM-R); (343:) advanced glycosylation end product-specific receptor isoform 1precursor [Homo sapiens]; (344:) advanced glycosylation end product-specific receptor isoform 2precursor [Homo sapiens];

(345:) aggrecanase 1 [Homo sapiens]; (346:) AHCYL1 protein [Homo sapiens]; (347:) AICAR formyltransferase/IMP cyclohydrolase bifunctional enzyme; (348:) AK001663 hypothetical protein [Homo sapiens]; (349:) A-kinase anchor protein 10 precursor [Homo sapiens]; (350:) A-kinase anchor protein 5 (A-kinase anchor protein 79 kDa) (AKAP79) (cAMP-dependent protein kinase regulatory subunit II highaffinity-binding protein) (H21); (351:) A-kinase anchor protein 7 isoform alpha [Homo sapiens]; (352:) A-kinase anchor protein 7 isoform beta [Homo sapiens]; (353:) A-kinase anchor protein 7 isoform gamma [Homo sapiens]; (354:) A-kinase anchor protein 8 [Homo sapiens]; (355:) alanyl-tRNA synthetase [Homo sapiens]; (356:) albumin precursor [Homo sapiens]; (357:) Alcohol dehydrogenase [NADP+] (Aldehyde reductase) (Aldo-ketoreductase family 1 member A1); (358:) Alcohol dehydrogenase 1B (Alcohol dehydrogenase beta subunit); (359:) alcohol dehydrogenase 1B (class I), beta polypeptide [Homosapiens]; (360:) Alcohol dehydrogenase 4 (Alcohol dehydrogenase class II pi chain); (361:) Alcohol dehydrogenase class 4 mu/sigma chain (Alcohol dehydrogenaseclass IV mu/sigma chain) (Retinol dehydrogenase) (Gastric alcoholdehydrogenase); (362:) alcohol dehydrogenase pi subunit; (363:) alcohol dehydrogenase, iron containing, 1 isoform 1 [Homo sapiens]; (364:) alcohol dehydrogenase, iron containing, 1 isoform 2 [Homo sapiens]; (365:) "alcohol sulfotransferase; hydroxysteroid sulfotransferase [Homosapiens]."; (366:) aldehyde dehydrogenase (NAD+) [Homo sapiens]; (367:) aldehyde dehydrogenase 1 (EC 1.2.1.3); (368:) aldehyde dehydrogenase 1 family, member L1 [Homo sapiens]; (369:) aldehyde dehydrogenase 1A1 [Homo sapiens]; (370:) aldehyde dehydrogenase 1A2 isoform 1 [Homo sapiens]; (371:) aldehyde dehydrogenase 1A2 isoform 2 [Homo sapiens]; (372:) aldehyde dehydrogenase 1A2 isoform 3 [Homo sapiens]; (373:) Aldehyde dehydrogenase 1A3 (Aldehyde dehydrogenase 6)(Retinaldehyde dehydrogenase 3) (RALDH-3); (374:) aldehyde dehydrogenase 1B1 precursor [Homo sapiens]; (375:) aldehyde dehydrogenase 2 (EC 1.2.1.3); (376:) aldehyde dehydrogenase 3 family, member A1 [Homo sapiens]; (377:) aldehyde dehydrogenase 4A1 precursor [Homo sapiens]; (378:) aldehyde dehydrogenase 5A1 precursor, isoform 1 [Homo sapiens]; (379:) aldehyde dehydrogenase 5A1 precursor, isoform 2 [Homo sapiens]; (380:) aldehyde dehydrogenase 6A1 precursor [Homo sapiens]; (381:) aldehyde dehydrogenase 8A1 isoform 1 [Homo sapiens]; (382:) aldehyde dehydrogenase 8A1 isoform 2 [Homo sapiens]; (383:) aldehyde dehydrogenase 9A1 [Homo sapiens]; (384:) Aldehyde dehydrogenase, dimeric NADP-preferring (ALDH class 3)(ALDHIII); (385:) Aldehyde dehydrogenase, mitochondrial precursor (ALDH class 2)(ALDHI) (ALDH-

E2); (386:) Aldehyde Reductase; (387:) Aldo-keto reductase family 1 member C3(Trans-1,2-dihydrobenzene-1,2-diol dehydrogenase)(3-alpha-hydroxysteroid dehydrogenase type 2) (3-alpha-HSD type 2)(3-alpha-HSD type II, brain) (Prostaglandin F synthase) (PGFS)(Estradiol 17-beta-dehydrogenase) (17-beta-hydroxysteroiddehydrogenase type 5) (17-beta-HSD 5) (Chlordecone reductasehomolog HAKRb) (HA1753) (Dihydrodiol dehydrogenase type I)(Dihydrodiol dehydrogenase 3) (DD3) (DD-3); (388:) aldo-keto reductase family 1, member A1 [Homo sapiens]; (389:) aldo-keto reductase family 1, member B1 [Homo sapiens]; (390:) aldo-keto reductase family 1, member C1 [Homo sapiens]; (391:) aldo-keto reductase family 1, member C2 [Homo sapiens]; (392:) aldo-keto reductase family 1, member C3 [Homo sapiens]; (393:) aldo-keto reductase family 1, member C4 [Homo sapiens]; (394:) aldo-keto reductase family 1, member D1 [Homo sapiens]; (395:) aldolase A [Homo sapiens]; (396:) aldolase B [Homo sapiens]; (397:) Aldose reductase (AR) (Aldehyde reductase); (398:) Aldose Reductase (E.C.1.1.1.21) Mutant With Cys 298 Replaced By Ser(C298s) Complex With Nadph; (399:) Aldose Reductase (E.C.1.1.1.21) Mutant With Tyr 48 Replaced By His(Y48h) Complexed With Nadp+ And Citrate; (400:) ALK tyrosine kinase receptor precursor (Anaplastic lymphoma kinase)(CD246 antigen); (401:) Alkaline ceramidase 1 (Alkaline CDase-1) (AlkCDase 1)(Acylsphingosine deacylase 3) (N-acylsphingosine amidohydrolase 3); (402:) Alkaline phosphatase, placental type precursor (PLAP-1) (Reganisozyme); (403:) Alkaline phosphatase, tissue-nonspecific isozyme precursor(AP-TNAP) (Liver/bone/kidney isozyme) (TNSALP); (404:) Alkaline phytoceramidase (aPHC) (Alkaline ceramidase) (Alkalinedihydroceramidase SB89); (405:) alkaline phytoceramidase [Homo sapiens]; (406:) alkyldihydroxyacetone phosphate synthase precursor [Homo sapiens]; (407:) Alkyldihydroxyacetonephosphate synthase, peroxisomal precursor(Alkyl-DHAP synthase) (Alkylglycerone-phosphate synthase)(Aging-associated protein 5); (408:) alpha (1, 2) fucosyltransferase [Homo sapiens]; (409:) alpha 1 type I collagen preproprotein [Homo sapiens]; (410:) alpha 1 type II collagen isoform 1 precursor [Homo sapiens]; (411:) alpha 1 type II collagen isoform 2 precursor [Homo sapiens]; (412:) alpha 1,2-mannosidase [Homo sapiens]; (413:) alpha 1,4-galactosyltransferase [Homo sapiens]; (414:) alpha 2,3-sialyltransferase III isoform A7 [Homo sapiens]; (415:) alpha 2,3-sialyltransferase III isoform A8 [Homo sapiens]; (416:) alpha 2,3-sialyltransferase III type D2+26 [Homo sapiens]; (417:) alpha galactosidase A; (418:) alpha isoform of regulatory subunit A, protein phosphatase 2 [Homosapiens]; (419:) alpha isoform of regulatory subunit B55,

protein phosphatase 2[Homo sapiens]; (420:) alpha mannosidase II; (421:) Alpha platelet-derived growth factor receptor precursor(PDGF-R-alpha) (CD140a antigen); (422:) alpha(1,2)fucosyltransferase [Homo sapiens]; (423:) Alpha-(1,3)-fucosyltransferase (Galactoside 3-L-fucosyltransferase)(Fucosyltransferase 6) (FUCT-VI); (424:) alpha/beta hydrolase domain containing protein 1 [Homo sapiens]; (425:) alpha-1 antitrypsin [Homo sapiens]; (426:) alpha-1 antitrypsin variant [Homo sapiens]; (427:) alpha-1,3(6)-mannosylglycoproteinbeta-1,6-N-acetyl-glucosaminyltransferase [Homo sapiens]; (428:) Alpha-1,4-N-acetylglucosaminyltransferase (Alpha4GnT); (429:) Alpha-1A adrenergic receptor (Alpha 1A-adrenoceptor) (Alpha1A-adrenoreceptor) (Alpha-1C adrenergic receptor) (Alpha adrenergicreceptor 1c); (430:) Alpha-1-antichymotrypsin precursor (ACT) [Contains:Alpha-1-antichymotrypsin His-Pro-less]; (431:) Alpha-1B adrenergic receptor (Alpha 1B-adrenoceptor) (Alpha1B-adrenoreceptor); (432:) Alpha-1D adrenergic receptor (Alpha 1D-adrenoceptor) (Alpha1D-adrenoreceptor) (Alpha-1A adrenergic receptor) (Alpha adrenergicreceptor 1a); (433:) Alpha-2A adrenergic receptor (Alpha-2A adrenoceptor) (Alpha-2Aadrenoreceptor) (Alpha-2AAR) (Alpha-2 adrenergic receptor subtypeC10); (434:) Alpha-2B adrenergic receptor (Alpha-2B adrenoceptor) (Alpha-2Badrenoreceptor) (Alpha-2 adrenergic receptor subtype C2); (435:) Alpha-2C adrenergic receptor (Alpha-2C adrenoceptor) (Alpha-2Cadrenoreceptor) (Alpha-2 adrenergic receptor subtype C4); (436:) Alpha-2-macroglobulin precursor (Alpha-2-M); (437:) alpha-2-macroglobulin precursor [Homo sapiens]; (438:) alpha-2-plasmin inhibitor [Homo sapiens]; (439:) alpha2-subunit of soluble guanylyl cyclase [Homo sapiens]; (440:) alpha-aminoadipate semialdehyde synthase [Homo sapiens]; (441:) "Alpha-aminoadipic semialdehyde synthase, mitochondrial precursor(LKR/SDH) [Includes:) Lysine ketoglutarate reductase (LOR) (LKR);Saccharopine dehydrogenase (SDH)]."; (442:) Alpha-enolase (2-phospho-D-glycerate hydro-lyase) (Non-neuralenolase) (NNE) (Enolase 1) (Phosphopyruvate hydratase) (C-mycpromoter-binding protein) (MBP-1) (MPB-1) (Plasminogen-bindingprotein); (443:) alpha-galactosidase A [Homo sapiens]; (444:) alpha-galactosidase A precursor (EC 3.2.1.22); (445:) Alpha-galactosidase A precursor (Melibiase) (Alpha-D-galactosidegalactohydrolase) (Alpha-D-galactosidase A) (Agalsidase alfa); (446:) alpha-galactosidase; (447:) alpha-keto acid dehydrogenase precursor; (448:) "alpha-ketoglutarate dehydrogenase complex dihydrolipoylsuccinyltransferase; KGDHC E2k component [Homo sapiens]."; (449:) alpha-KG-E2 [Homo sapiens]; (450:) Alpha-lactalbumin precursor (Lactose synthase B protein); (451:) alpha-L-iduronidase precursor [Homo sapiens]; (452:) Alpha-L-

iduronidase precursor; (453:) alpha-methylacyl-CoA racemase isoform 1 [Homo sapiens]; (454:) alpha-methylacyl-CoA racemase isoform 2 [Homo sapiens]; (455:) alpha-N-acetylgalactosaminidase precursor [Homo sapiens]; (456:) alpha-N-acetylglucosaminidase precursor [Homo sapiens]; (457:) alpha-N-acetylglucosaminidase; (458:) Alpha-N-acetylneuraminide alpha-2,8-sialyltransferase (Ganglioside GD3 synthase) (Ganglioside GT3 synthase)(Alpha-2,8-sialyltransferase 8A) (ST8Sia I); (459:) alpha-synuclein isoform NACP112 [Homo sapiens]; (460:) alpha-synuclein isoform NACP140 [Homo sapiens]; (461:) amiloride binding protein [Homo sapiens]; (462:) Amiloride binding protein 1 (amine oxidase (copper-containing))[Homo sapiens]; (463:) amiloride binding protein 1 precursor [Homo sapiens]; (464:) amiloride-binding protein 1 (amine oxidase (copper-containing))[Homo sapiens]; (465:) amiloride-binding protein; (466:) Amiloride-sensitive amine oxidase [copper-containing] precursor(Diamine oxidase) (DAO) (Amiloride-binding protein) (ABP)(Histaminase) (Kidney amine oxidase) (KAO); (467:) amine oxidase (flavin containing) domain 2 isoform b [Homosapiens]; (468:) amine oxidase (flavin-containing) [Homo sapiens]; (469:) Amine oxidase [flavin-containing] A (Monoamine oxidase type A)(MAO-A); (470:) amine oxidase, copper containing 2 (retina-specific) [Homosapiens]; (471:) amine oxidase, copper containing 2 isoform a [Homo sapiens]; (472:) amine oxidase, copper containing 2 isoform b [Homo sapiens]; (473:) Amine oxidase, copper containing 3 (vascular adhesion protein 1)[Homo sapiens]; (474:) amine oxidase, copper containing 3 precursor [Homo sapiens]; (475:) amino-acid N-acetyltransferase (EC 2.3.1.1) - human; (476:) aminoacylase 1 [Homo sapiens]; (477:) aminoadipate-semialdehyde dehydrogenase-phosphopantetheinyltransferase [Homo sapiens]; (478:) aminoadipate-semialdehyde synthase [Homo sapiens]; (479:) aminocarboxymuconate semialdehyde decarboxylase [Homo sapiens]; (480:) aminolevulinate delta-synthase 1 [Homo sapiens]; (481:) aminolevulinate, delta, synthase 1 [Homo sapiens]; (482:) Aminolevulinate, delta-, synthase 1 [Homo sapiens]; (483:) aminolevulinate, delta-, synthase 2 isoform a [Homo sapiens]; (484:) aminolevulinate, delta-, synthase 2 isoform b [Homo sapiens]; (485:) aminolevulinate, delta-, synthase 2 isoform c [Homo sapiens]; (486:) aminolevulinate, delta-, synthase 2 isoform d [Homo sapiens]; (487:) aminomethyltransferase (glycine cleavage system protein T) [Homosapiens]; (488:) Aminopeptidase N (hAPN) (Alanyl aminopeptidase) (Microsomalaminopeptidase) (Aminopeptidase M) (gp150) (Myeloid plasma membraneglycoprotein CD13) (CD13 antigen); (489:) Aminopeptidase O (AP-O); (490:) aminopeptidase puromycin

sensitive [Homo sapiens]; (491:) AMP deaminase 3 (AMP deaminase isoform E) (Erythrocyte AMPdeaminase); (492:) AMP-activated protein kinase alpha 2 catalytic subunit [Homosapiens]; (493:) AMP-activated protein kinase beta 1 non-catalytic subunit [Homosapiens]; (494:) AMP-activated protein kinase beta 2 non-catalytic subunit [Homosapiens]; (495:) AMP-activated protein kinase gamma2 subunit isoform a [Homosapiens]; (496:) AMP-activated protein kinase gamma2 subunit isoform b [Homosapiens]; (497:) AMP-activated protein kinase gamma2 subunit isoform c [Homosapiens]; (498:) AMP-activated protein kinase, noncatalytic gamma-1 subunit isoform1 [Homo sapiens]; (499:) AMP-activated protein kinase, noncatalytic gamma-1 subunit isoform2 [Homo sapiens]; (500:) AMP-activated protein kinase, non-catalytic gamma-3 subunit [Homosapiens]; (501:) AMP-binding enzyme, 33217 [Homo sapiens]; (502:) amphiregulin preproprotein [Homo sapiens]; (503:) "amylase, alpha 1A; salivary precursor [Homo sapiens]."; (504:) Amylo-1, 6-glucosidase, 4-alpha-glucanotransferase (glycogendebranching enzyme, glycogen storage disease type III) [Homosapiens]; (505:) amylo-1, 6-glucosidase, 4-alpha-glucanotransferase isoform 1 [Homosapiens]; (506:) amylo-1, 6-glucosidase, 4-alpha-glucanotransferase isoform 2 [Homosapiens]; (507:) amylo-1, 6-glucosidase, 4-alpha-glucanotransferase isoform 3 [Homosapiens]; (508:) "Amyloid beta A4 protein precursor (APP) (ABPP) (Alzheimer diseaseamyloid protein) (Cerebral vascular amyloid peptide) (CVAP)(Protease nexin-II) (PN-II) (APPI) (PreA4) [Contains:) SolubleAPP-alpha (S-APP-alpha); Soluble APP-beta (S-APP-beta); C99;Beta-amyloid protein 42 (Beta-APP42); Beta-amyloid protein 40(Beta-APP40); C83; P3(42); P3(40); Gamma-CTF(59) (Gamma-secretaseC-terminal fragment 59) (Amyloid intracellular domain 59)(AID(59)); Gamma-CTF(57) (Gamma-secretase C-terminal fragment 57)(Amyloid intracellular domain 57) (AID(57)); Gamma-CTF(50)(Gamma-secretase C-terminal fragment 50) (Amyloid intracellulardomain 50) (AID(50)); C31]."; (509:) amyloid beta A4 protein precursor, isoform a [Homo sapiens]; (510:) amyloid beta A4 protein precursor, isoform b [Homo sapiens]; (511:) amyloid beta A4 protein precursor, isoform c [Homo sapiens]; (512:) Amyloid beta precursor protein binding protein 1 [Homo sapiens]; (513:) amyloid beta precursor protein-binding protein 1 isoform a [Homosapiens]; (514:) amyloid beta precursor protein-binding protein 1 isoform b [Homosapiens]; (515:) amyloid beta precursor protein-binding protein 1 isoform c [Homosapiens]; (516:) amyloid precursor protein-binding protein 1 (APP-B1) [Homosapiens]; (517:) amyloid precursor protein-binding protein 1; (518:) anaphase promoting complex subunit 1 [Homo sapiens]; (519:) anaphase promoting complex subunit 10 [Homo sapiens]; (520:) Anaphase-

promoting complex subunit 11 (APC11) (Cyclosome subunit11) (Hepatocellular carcinoma-associated RING finger protein); (521:) anaphase-promoting complex subunit 2 [Homo sapiens]; (522:) anaphase-promoting complex subunit 4 [Homo sapiens]; (523:) anaphase-promoting complex subunit 5 [Homo sapiens]; (524:) anaphase-promoting complex subunit 7 [Homo sapiens]; (525:) Androgen receptor (Dihydrotestosterone receptor); (526:) androgen receptor isoform 1 [Homo sapiens]; (527:) androgen receptor isoform 2 [Homo sapiens]; (528:) androgen-regulated short-chain dehydrogenase/reductase 1 [Homosapiens]; (529:) Angiogenin precursor (Ribonuclease 5) (RNase 5); (530:) Angiopoietin-1 receptor precursor (Tyrosine-protein kinase receptorTIE-2) (hTIE2) (Tyrosine-protein kinase receptor TEK) (p140 TEK)(Tunica interna endothelial cell kinase) (CD202b antigen); (531:) angiotensin converting enzyme (EC 3.4.15.1); (532:) angiotensin converting enzyme 2 [Homo sapiens]; (533:) angiotensin converting enzyme precursor (EC 3.4.15.1); (534:) angiotensin converting enzyme-like protein [Homo sapiens]; (535:) angiotensin I converting enzyme (peptidyl-dipeptidase A) 1 [Homosapiens]; (536:) Angiotensin I converting enzyme (peptidyl-dipeptidase A) 2 [Homosapiens]; (537:) angiotensin I converting enzyme [Homo sapiens]; (538:) angiotensin I converting enzyme 2 precursor [Homo sapiens]; (539:) angiotensin I converting enzyme isoform 1 precursor [Homo sapiens]; (540:) angiotensin I converting enzyme isoform 1 precursor variant [Homosapiens]; (541:) angiotensin I converting enzyme isoform 2 precursor [Homo sapiens]; (542:) angiotensin I converting enzyme isoform 3 precursor [Homo sapiens]; (543:) "angiotensin I converting enzyme precursor; dipeptidylcarboxypeptidase 1 [Homo sapiens]."; (544:) "angiotensin I converting enzyme precursor; dipeptidylcarboxypeptidase 1; kininase II [Homo sapiens]."; (545:) angiotensin I-converting enzyme [Homo sapiens]; (546:) angiotensin I-converting enzyme precursor (EC 3.4.15.1); (547:) angiotensin II receptor type-1 (clone HATR1GH) - human (fragment); (548:) angiotensin II receptor, type 1 [Homo sapiens]; (549:) angiotensin II receptor, type 2 [Homo sapiens]; (550:) angiotensin-converting enzyme [Homo sapiens]; (551:) angiotensin-converting enzyme 2 [Homo sapiens]; (552:) Angiotensin-converting enzyme 2 precursor (ACE-relatedcarboxypeptidase) (Angiotensin-converting enzyme homolog) (ACEH); (553:) Angiotensin-converting enzyme, somatic isoform precursor(Dipeptidyl carboxypeptidase I) (Kininase II) (CD143 antigen)[Contains:) Angiotensin-converting enzyme, somatic isoform, solubleform]; (554:) Angiotensin-converting enzyme, testis-specific isoform precursor(ACE-T) (Dipeptidyl carboxypeptidase I) (Kininase II) [Contains:Angiotensin-converting enzyme, testis-specific isoform, solubleform];

(555:) "Angiotensinogen precursor [Contains:) Angiotensin-1 (Angiotensin I)(Ang I); Angiotensin-2 (Angiotensin II) (Ang II); Angiotensin-3(Angiotensin III) (Ang III) (Des-Asp[1]-angiotensin II)]."; (556:) angiotensinogen preproprotein [Homo sapiens]; (557:) Annexin A4 (Annexin IV) (Lipocortin IV) (Endonexin I)(Chromobindin-4) (Protein II) (P32.5) (Placental anticoagulantprotein II) (PAP-II) (PP4-X) (35-beta calcimedin)(Carbohydrate-binding protein P33/P41) (P33/41); (558:) Annexin A5 (Annexin V) (Lipocortin V) (Endonexin II) (CalphobindinI) (CBP-I) (Placental anticoagulant protein I) (PAP-I) (PP4)(Thromboplastin inhibitor) (Vascular anticoagulant-alpha)(VAC-alpha) (Anchorin CII); (559:) anthracycline-associated resistance ARX [Homo sapiens]; (560:) Anthrax toxin receptor 1 precursor (Tumor endothelial marker 8); (561:) Anthrax toxin receptor 2 precursor (Capillary morphogenesis gene 2protein) (CMG-2); (562:) Anti-Muellerian hormone type-2 receptor precursor (Anti-Muellerianhormone type II receptor) (AMH type II receptor) (MIS type IIreceptor) (MISRII) (MRII); (563:) antioxidant enzyme AOE37-2 [Homo sapiens]; (564:) antioxidant enzyme B166 [Homo sapiens]; (565:) AP2-associated protein kinase 1 (Adaptor-associated kinase 1); (566:) APC11 anaphase promoting complex subunit 11 isoform 1 [Homosapiens]; (567:) APC11 anaphase promoting complex subunit 11 isoform 2 [Homosapiens]; (568:) Apelin receptor (G-protein coupled receptor APJ) (Angiotensinreceptor-like 1) (HG11); (569:) APEX nuclease (multifunctional DNA repair enzyme) [Homo sapiens]; (570:) APEX nuclease (multifunctional DNA repair enzyme) 1 [Homo sapiens]; (571:) APG10 autophagy 10-like [Homo sapiens]; (572:) APG12 autophagy 12-like [Homo sapiens]; (573:) Apg3p [Homo sapiens]; (574:) APG4 autophagy 4 homolog B isoform a [Homo sapiens]; (575:) APG4 autophagy 4 homolog B isoform b [Homo sapiens]; (576:) APG5 autophagy 5-like [Homo sapiens]; (577:) APG7 autophagy 7-like [Homo sapiens]; (578:) APOBEC1 complementation factor (APOBEC1-stimulating protein); (579:) apobec-1 complementation factor isoform 1 [Homo sapiens]; (580:) apobec-1 complementation factor isoform 2 [Homo sapiens]; (581:) apobec-1 complementation factor isoform 3 [Homo sapiens]; (582:) APOBEC-1 stimulating protein [Homo sapiens]; (583:) Apolipoprotein A-I precursor (Apo-AI) (ApoA-I) [Contains:Apolipoprotein A-I(1-242)]; (584:) apolipoprotein A-II preproprotein [Homo sapiens]; (585:) apolipoprotein B mRNA editing enzyme [Homo sapiens]; (586:) apolipoprotein B mRNA editing enzyme catalytic polypeptide-like 3G[Homo sapiens]; (587:) apolipoprotein B mRNA editing enzyme complex-1 [Homo sapiens]; (588:) apolipoprotein B mRNA editing enzyme, catalytic polypeptide 1; (589:) apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 2[Homo sapiens];

(590:) apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 2variant [Homo sapiens]; (591:) Apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3A[Homo sapiens]; (592:) apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3B[Homo sapiens]; (593:) apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3C[Homo sapiens]; (594:) apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3Cvariant [Homo sapiens]; (595:) apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3D[Homo sapiens]; (596:) Apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3F[Homo sapiens]; (597:) apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3Fisoform a [Homo sapiens]; (598:) apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3Fisoform b [Homo sapiens]; (599:) apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3G[Homo sapiens]; (600:) Apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3H[Homo sapiens]; (601:) apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 4(putative) [Homo sapiens]; (602:) apolipoprotein B precursor [Homo sapiens]; (603:) apolipoprotein C-II precursor [Homo sapiens]; (604:) apolipoprotein D precursor [Homo sapiens]; (605:) apolipoprotein E precursor [Homo sapiens]; (606:) apoptotic caspase Mch5-beta [Homo sapiens]; (607:) apoptotic cysteine protease Mch5 isoform alpha; (608:) apoptotic cysteine protease proMch4; (609:) aprataxin isoform a [Homo sapiens]; (610:) aprataxin isoform b [Homo sapiens]; (611:) aprataxin isoform c [Homo sapiens]; (612:) aprataxin isoform d [Homo sapiens]; (613:) apurinic/apyrimidinic endonuclease; (614:) aquaporin 12A [Homo sapiens]; (615:) arachidonate 12-lipoxygenase [Homo sapiens]; (616:) arachidonate 15-lipoxygenase [Homo sapiens]; (617:) arachidonate 5-lipoxygenase [Homo sapiens]; (618:) arachidonate 5-lipoxygenase-activating protein [Homo sapiens]; (619:) Archaemetzincin-1 (Archeobacterial metalloproteinase-like protein1); (620:) Archaemetzincin-2 (Archeobacterial metalloproteinase-like protein2); (621:) arginase, type I [Homo sapiens]; (622:) Arginine decarboxylase (ARGDC) (ADC) (Ornithine decarboxylase-likeprotein) (ODC-paralogue) (ODC-p); (623:) arginine decarboxylase [Homo sapiens]; (624:) arginine methyltransferase 6 [Homo sapiens]; (625:) argininosuccinate lyase isoform 1 [Homo sapiens]; (626:) argininosuccinate lyase isoform 2 [Homo sapiens]; (627:) argininosuccinate lyase isoform 3 [Homo sapiens]; (628:) arginyl aminopeptidase (aminopeptidase B) [Homo sapiens]; (629:) arginyltransferase 1 isoform 1 [Homo sapiens]; (630:) arginyltransferase 1 isoform 2 [Homo sapiens]; (631:) Ariadne homolog, ubiquitin-conjugating enzyme E2 binding protein, 1(Drosophila) [Homo sapiens]; (632:)

ariadne ubiquitin-conjugating enzyme E2 binding protein homolog 1[Homo sapiens]; (633:) aromatase cytochrome P-450; (634:) aromatic decarboxylase [Homo sapiens]; (635:) Aromatic-L-amino-acid decarboxylase (AADC) (DOPA decarboxylase)(DDC); (636:) Arsenite methyltransferase (S-adenosyl-L-methionine:arsenic(III)methyltransferase) (Methylarsonite methyltransferase); (637:) Aryl hydrocarbon receptor precursor (Ah receptor) (AhR); (638:) Arylacetamide deacetylase (AADAC); (639:) arylalkylamine N-acetyltransferase [Homo sapiens]; (640:) arylamide acetylase 2 [Homo sapiens]; (641:) Arylamine N-acetyltransferase 1 (Arylamide acetylase 1)(Monomorphic arylamine N-acetyltransferase) (MNAT)(N-acetyltransferase type 1) (NAT-1); (642:) "Arylsulfatase A precursor (ASA) (Cerebroside-sulfatase) [Contains:Arylsulfatase A component B; Arylsulfatase A component C]."; (643:) arylsulfatase A precursor [Homo sapiens]; (644:) arylsulfatase B isoform 1 precursor [Homo sapiens]; (645:) arylsulfatase B isoform 2 precursor [Homo sapiens]; (646:) Arylsulfatase B precursor (ASB) (N-acetylgalactosamine-4-sulfatase)(G4S); (647:) Arylsulfatase E precursor (ASE); (648:) Arylsulfatase F precursor (ASF); (649:) Asialoglycoprotein receptor 1 (ASGPR 1) (ASGP-R 1) (Hepatic lectinH1); (650:) Asialoglycoprotein receptor 2 (ASGP-R 2) (ASGPR 2) (Hepatic lectinH2); (651:) asparagine-linked glycosylation 12 [Homo sapiens]; (652:) aspartate aminotransferase 1 [Homo sapiens]; (653:) aspartate aminotransferase 2 precursor [Homo sapiens]; (654:) aspartoacylase [Homo sapiens]; (655:) aspartylglucosaminidase precursor [Homo sapiens]; (656:) aspartyl-tRNA synthetase [Homo sapiens]; (657:) Astacin-like metalloendopeptidase precursor (Oocyte astacin)(Ovastacin); (658:) ataxin 3 isoform 1 [Homo sapiens]; (659:) ataxin 3 isoform 2 [Homo sapiens]; (660:) ataxin 3 isoform 3 [Homo sapiens]; (661:) Ataxin-3 (Machado-Joseph disease protein 1) (Spinocerebellar ataxiatype 3 protein); (662:) ATP citrate lyase isoform 1 [Homo sapiens]; (663:) ATP citrate lyase isoform 2 [Homo sapiens]; (664:) ATP specific succinyl CoA synthetase beta subunit precursor [Homosapiens]; (665:) ATP sulfurylase/APS kinase [Homo sapiens]; (666:) ATP sulfurylase/APS kinase isoform SK2 [Homo sapiens]; (667:) ATP synthase mitochondrial F1 complex assembly factor 1 isoform 1 precursor [Homo sapiens]; (668:) ATP synthase mitochondrial F1 complex assembly factor 1 isoform 2 precursor [Homo sapiens]; (669:) ATP synthase mitochondrial F1 complex assembly factor 2 [Homosapiens]; (670:) ATPase, Ca++ transporting, cardiac muscle, slow twitch 2 isoform 1[Homo sapiens]; (671:) ATPase, Ca++ transporting, cardiac muscle, slow twitch 2 isoform 2[Homo sapiens]; (672:) ATPase, Ca++ transporting, fast twitch 1 isoform a [Homo sapiens]; (673:) ATPase, Ca++

transporting, fast twitch 1 isoform b [Homo sapiens]; (674:) ATPase, Cu++ transporting, alpha polypeptide [Homo sapiens]; (675:) ATPase, Cu++ transporting, beta polypeptide isoform a [Homosapiens]; (676:) ATPase, Cu++ transporting, beta polypeptide isoform b [Homosapiens]; (677:) ATPase, H+ transporting, lysosomal 14kD, V1 subunit F [Homosapiens]; (678:) ATPase, H+ transporting, lysosomal 21kDa, V0 subunit b isoform 1[Homo sapiens]; (679:) ATPase, H+ transporting, lysosomal 21kDa, V0 subunit b isoform 2[Homo sapiens]; (680:) ATPase, H+ transporting, lysosomal 42kDa, V1 subunit C1 isoform A[Homo sapiens]; (681:) ATPase, H+ transporting, lysosomal 42kDa, V1 subunit C1 isoform B[Homo sapiens]; (682:) ATPase, H+ transporting, lysosomal 50/57kDa, V1 subunit H [Homosapiens]; (683:) ATPase, H+ transporting, lysosomal 50/57kDa, V1 subunit H isoform 1[Homo sapiens]; (684:) ATPase, H+ transporting, lysosomal 50/57kDa, V1 subunit H isoform 2[Homo sapiens]; (685:) ATPase, H+ transporting, lysosomal 56/58kDa, V1 subunit B1 [Homosapiens]; (686:) ATPase, H+ transporting, lysosomal 70kD, V1 subunit A, isoform 1[Homo sapiens]; (687:) ATPase, H+ transporting, lysosomal 9kDa, V0 subunit e1 [Homosapiens]; (688:) ATPase, H+ transporting, lysosomal accessory protein 1 precursor[Homo sapiens]; (689:) ATPase, H+ transporting, lysosomal V0 subunit a isoform 1 [Homosapiens]; (690:) ATPase, H+ transporting, lysosomal V0 subunit a4 [Homo sapiens]; (691:) ATPase, H+ transporting, lysosomal, V0 subunit c [Homo sapiens]; (692:) ATPase, H+ transporting, lysosomal, V0 subunit d1 [Homo sapiens]; (693:) ATPase, H+ transporting, lysosomal, V1 subunit G2 isoform a [Homosapiens]; (694:) ATPase, H+ transporting, lysosomal, V1 subunit G2 isoform b [Homosapiens]; (695:) ATPase, H+ transporting, lysosomal, V1 subunit G3 isoform a [Homosapiens]; (696:) ATPase, H+ transporting, lysosomal, V1 subunit G3 isoform b [Homosapiens]; (697:) ATPase, H+/K+ exchanging, alpha polypeptide [Homo sapiens]; (698:) ATPase, H+/K+ exchanging, beta polypeptide [Homo sapiens]; (699:) ATP-binding cassette sub-family B member 1 [Homo sapiens]; (700:) ATP-binding cassette transporter sub-family C member 8(Sulfonylurea receptor 1); (701:) ATP-binding cassette transporter sub-family C member 9(Sulfonylurea receptor 2); (702:) ATP-citrate synthase (ATP-citrate (pro-S-)-lyase) (Citrate cleavageenzyme); (703:) ATP-dependent DNA helicase 2 subunit 1 (ATP-dependent DNA helicaseII 70 kDa subunit) (Lupus Ku autoantigen protein p70) (Ku70) (70kDa subunit of Ku antigen) (Thyroid-lupus autoantigen) (TLAA) (CTCbox-binding factor 75 kDa subunit) (CTCBF) (CTC75) (DNA-repairprotein XRCC6); (704:) ATP-dependent DNA helicase 2 subunit 2 (ATP-dependent DNA helicaseII 80 kDa subunit) (Lupus

Ku autoantigen protein p86) (Ku86) (Ku80)(86 kDa subunit of Ku antigen) (Thyroid-lupus autoantigen) (TLAA)(CTC box-binding factor 85 kDa subunit) (CTCBF) (CTC85) (Nuclearfactor IV) (DNA-repair protein XRCC5); (705:) ATP-dependent DNA helicase II [Homo sapiens]; (706:) ATP-dependent DNA helicase II, 70 kDa subunit [Homo sapiens]; (707:) Atrial natriuretic peptide clearance receptor precursor (ANP-C)(ANPRC) (NPR-C) (Atrial natriuretic peptide C-type receptor); (708:) Atrial natriuretic peptide receptor A precursor (ANP-A) (ANPRA)(GC-A) (Guanylate cyclase) (NPR-A) (Atrial natriuretic peptideA-type receptor); (709:) Atrial natriuretic peptide receptor B precursor (ANP-B) (ANPRB)(GC-B) (Guanylate cyclase B) (NPR-B) (Atrial natriuretic peptideB-type receptor); (710:) Atrial natriuteric peptide-converting enzyme (pro-ANP-convertingenzyme) (Corin) (Heart-specific serine proteinase ATC2)(Transmembrane protease, serine 10); (711:) Attractin precursor (Mahogany homolog) (DPPT-L); (712:) AU RNA-binding protein/enoyl-Coenzyme A hydratase precursor [Homosapiens]; (713:) Autocrine motility factor receptor precursor, isoform 1 (AMFreceptor); (714:) Autocrine motility factor receptor, isoform 2 (AMF receptor)(gp78); (715:) autoimmune regulator AIRE isoform 1 [Homo sapiens]; (716:) autoimmune regulator AIRE isoform 2 [Homo sapiens]; (717:) Autophagy-related protein 10 (APG10-like); (718:) Autophagy-related protein 3 (APG3-like) (hApg3) (Protein PC3-96); (719:) Autophagy-related protein 7 (APG7-like) (Ubiquitin-activatingenzyme E1-like protein) (hAGP7); (720:) autotaxin isoform 1 preproprotein [Homo sapiens]; (721:) autotaxin isoform 2 preproprotein [Homo sapiens]; (722:) Azurocidin precursor (Cationic antimicrobial protein CAP37)(Heparin-binding protein) (HBP); (723:) azurocidin, PUP=elastase homlog [human, Peptide Partial, 21 aa]; (724:) B- and T-lymphocyte attenuator precursor (B- andT-lymphocyte-associated protein) (CD272 antigen); (725:) B1 bradykinin receptor (BK-1 receptor) (B1R); (726:) B2 bradykinin receptor (BK-2 receptor) (B2R); (727:) B3GAT1 [Homo sapiens]; (728:) B3GAT2 [Homo sapiens]; (729:) B3GAT2 protein [Homo sapiens]; (730:) B3GAT3 protein [Homo sapiens]; (731:) baculoviral IAP repeat-containing 6 [Homo sapiens]; (732:) Baculoviral IAP repeat-containing protein 6 (Ubiquitin-conjugatingBIR-domain enzyme apollon); (733:) Basic fibroblast growth factor receptor 1 precursor (FGFR-1)(bFGF-R) (Fms-like tyrosine kinase 2) (c-fgr) (CD331 antigen); (734:) BDNF/NT-3 growth factors receptor precursor (Neurotrophic tyrosinekinase receptor type 2) (TrkB tyrosine kinase) (GP145-TrkB)(Trk-B); (735:) beclin 1 [Homo sapiens]; (736:) beta adrenergic receptor kinase 1 [Homo sapiens]; (737:) beta adrenergic receptor kinase 2 [Homo sapiens]; (738:) beta amyloid cleaving enzyme 2 [Homo sapiens]; (739:) beta

isoform of regulatory subunit A, protein phosphatase 2 isoforma [Homo sapiens]; (740:) beta isoform of regulatory subunit A, protein phosphatase 2 isoformb [Homo sapiens]; (741:) beta isoform of regulatory subunit B55, protein phosphatase 2isoform a [Homo sapiens]; (742:) beta isoform of regulatory subunit B55, protein phosphatase 2isoform b [Homo sapiens]; (743:) beta isoform of regulatory subunit B55, protein phosphatase 2isoform c [Homo sapiens]; (744:) beta isoform of regulatory subunit B55, protein phosphatase 2isoform d [Homo sapiens]; (745:) beta isoform of regulatory subunit B56, protein phosphatase 2A[Homo sapiens]; (746:) Beta klotho (BetaKlotho) (Klotho beta-like protein); (747:) Beta platelet-derived growth factor receptor precursor(PDGF-R-beta) (CD140b antigen); (748:) beta(1,6)-N-acetylglucosaminyltransferase V isoform 1 [Homosapiens]; (749:) beta(1,6)-N-acetylglucosaminyltransferase V isoform 2 [Homosapiens]; (750:) Beta,beta-carotene 9',10'-dioxygenase (Beta-carotene dioxygenase 2)(B-diox-II); (751:) Beta-1 adrenergic receptor (Beta-1 adrenoceptor) (Beta-1adrenoreceptor); (752:) beta1,3 galactosyltransferase-V [Homo sapiens]; (753:) Beta-1,3-galactosyl-O-glycosyl-glycoproteinbeta-1,6-N-acetylglucosaminyltransferase (Core 2 branching enzyme)(Core2-GlcNAc-transferase) (C2GNT) (Core 2 GNT); (754:) beta-1,3-galactosyl-O-glycosyl-glycoproteinbeta-1,6-N-acetylglucosaminyltransferase [Homo sapiens]; (755:) beta1,3-galactosyltransferase [Homo sapiens]; (756:) Beta-1,3-galactosyltransferase 5 (Beta-1,3-GalTase 5) (Beta3Gal-T5)(b3Gal-T5) (UDP-galactose:beta-N-acetylglucosaminebeta-1,3-galactosyltransferase 5) (UDP-Gal:beta-GlcNAcbeta-1,3-galactosyltransferase 5) (Beta-3-Gx-T5); (757:) Beta-1,3-glucosyltransferase (Beta3Glc-T)(Beta-3-glycosyltransferase-like); (758:) Beta-1,3-glucuronyltransferase 1 (glucuronosyltransferase P) [Homosapiens]; (759:) beta-1,3-glucuronyltransferase 1 [Homo sapiens]; (760:) Beta-1,3-glucuronyltransferase 3 (glucuronosyltransferase I) [Homosapiens]; (761:) beta-1,3-glucuronyltransferase 3 [Homo sapiens]; (762:) beta1,3-N-acetylglucosaminyltransferase 5 [Homo sapiens]; (763:) beta-1,3-N-acetylglucosaminyltransferase 6 [Homo sapiens]; (764:) "Beta-1,4-galactosyltransferase 1 (Beta-1,4-GalTase 1) (Beta4Gal-T1)(b4Gal-T1) (UDP-galactose:beta-N-acetylglucosaminebeta-1,4-galactosyltransferase 1) (UDP-Gal:beta-GlcNAcbeta-1,4-galactosyltransferase 1) [Includes:) Lactose synthase Aprotein ; N-acetyllactosamine synthase (Nal synthetase);Beta-N-acetylglucosaminylglycopeptidebeta-1,4-galactosyltransferase ;Beta-N-acetylglucosaminyl-glycolipid beta-1,4-galactosyltransferase]."; (765:) Beta-1,4-galactosyltransferase 6 (Beta-1,4-GalTase 6) (Beta4Gal-T6)(b4Gal-T6) (UDP-galactose:beta-N-acetylglucosaminebeta-1,4-galactosyltransferase 6) (UDP-

Gal:beta-GlcNAcbeta-1,4-galactosyltransferase 6) [Includes:) Lactosylceramidesynthase (LacCer synthase) (UDP-Gal:glucosylceramidebeta-1,4-galactosyltransferase)]; (766:) beta-1,4-N-acethylgalactosaminyltransferase [Homo sapiens]; (767:) beta-1,4-N-acetyl-galactosaminyl transferase 1 [Homo sapiens]; (768:) beta-1,6-N-acetylglucosaminyltransferase [Homo sapiens]; (769:) beta-1,6-N-acetylglucosaminyltransferase 2 [Homo sapiens]; (770:) beta-1,6-N-acetylglucosaminyltransferase 3 [Homo sapiens]; (771:) beta-1,6-N-acetylglucosaminyltransferase; (772:) Beta-2 adrenergic receptor (Beta-2 adrenoceptor) (Beta-2adrenoreceptor); (773:) Beta-3 adrenergic receptor (Beta-3 adrenoceptor) (Beta-3adrenoreceptor); (774:) beta-adrenergic-receptor kinase (EC 2.7.1.126) 2 - human; (775:) Beta-Ala-His dipeptidase precursor (Carnosine dipeptidase 1) (CNDPdipeptidase 1) (Serum carnosinase) (Glutamate carboxypeptidase-likeprotein 2); (776:) beta-carotene 15, 15'-monooxygenase 1 [Homo sapiens]; (777:) beta-carotene dioxygenase 2 isoform a [Homo sapiens]; (778:) beta-carotene dioxygenase 2 isoform b [Homo sapiens]; (779:) beta-D-galactosidase precursor (EC 3.2.1.23); (780:) Beta-galactosidase precursor (Lactase) (Acid beta-galactosidase); (781:) beta-galactosidase related protein precursor; (782:) Beta-galactosidase-related protein precursor(Beta-galactosidase-like protein) (S-Gal) (Elastin-binding protein)(EBP); (783:) Beta-hexosaminidase alpha chain precursor(N-acetyl-beta-glucosaminidase) (Beta-N-acetylhexosaminidase)(Hexosaminidase A); (784:) "Beta-hexosaminidase beta chain precursor(N-acetyl-beta-glucosaminidase) (Beta-N-acetylhexosaminidase)(Hexosaminidase B) (Cervical cancer proto-oncogene 7) (HCC-7)[Contains:) Beta-hexosaminidase beta-B chain; Beta-hexosaminidasebeta-A chain]."; (785:) beta-hexosaminidase beta-chain {R to Q substitution at residue 505,internal fragment} {EC 3.2.1.53} [human, skin fibroblasts, PeptidePartial Mutant, 23 aa]; (786:) betaine-homocysteine methyltransferase [Homo sapiens]; (787:) beta-mannosidase [Homo sapiens]; (788:) beta-polymerase; (789:) Beta-secretase 1 precursor (Beta-site APP cleaving enzyme 1)(Beta-site amyloid precursor protein cleaving enzyme 1)(Membrane-associated aspartic protease 2) (Memapsin-2) (Aspartylprotease 2) (Asp 2) (ASP2); (790:) Beta-secretase 2 precursor (Beta-site APP-cleaving enzyme 2)(Aspartyl protease 1) (Asp 1) (ASP1) (Membrane-associated asparticprotease 1) (Memapsin-1) (Down region aspartic protease); (791:) beta-site APP cleaving enzyme [Homo sapiens]; (792:) beta-site APP cleaving enzyme I-432 [Homo sapiens]; (793:) beta-site APP cleaving enzyme I-457 [Homo sapiens]; (794:) beta-site APP cleaving enzyme I-476 [Homo sapiens]; (795:)

beta-site APP cleaving enzyme isoform I-127 [Homo sapiens]; (796:) beta-site APP cleaving enzyme type B [Homo sapiens]; (797:) beta-site APP cleaving enzyme type C [Homo sapiens]; (798:) beta-site APP-cleaving enzyme [Homo sapiens]; (799:) Beta-site APP-cleaving enzyme 1 [Homo sapiens]; (800:) beta-site APP-cleaving enzyme 1 isoform A preproprotein [Homosapiens]; (801:) beta-site APP-cleaving enzyme 1 isoform B preproprotein [Homosapiens]; (802:) beta-site APP-cleaving enzyme 1 isoform C preproprotein [Homosapiens]; (803:) beta-site APP-cleaving enzyme 1 isoform D preproprotein [Homosapiens]; (804:) Beta-site APP-cleaving enzyme 2 [Homo sapiens]; (805:) beta-site APP-cleaving enzyme 2 isoform A preproprotein [Homosapiens]; (806:) beta-site APP-cleaving enzyme 2 isoform B preproprotein [Homosapiens]; (807:) beta-site APP-cleaving enzyme 2 isoform C preproprotein [Homosapiens]; (808:) beta-site APP-cleaving enzyme 2, EC 3.4.23. [Homo sapiens]; (809:) beta-synuclein [Homo sapiens]; (810:) Beta-ureidopropionase (Beta-alanine synthase)(N-carbamoyl-beta-alanine amidohydrolase) (BUP-1); (811:) "Bifunctional 3'-phosphoadenosine 5'-phosphosulfate synthetase 1(PAPS synthetase 1) (PAPSS 1) (Sulfurylase kinase 1) (SK1) (SK 1)[Includes:) Sulfate adenylyltransferase (Sulfate adenylatetransferase) (SAT) (ATP-sulfurylase); Adenylyl-sulfate kinase(Adenylylsulfate 3'-phosphotransferase) (APS kinase)(Adenosine-5'-phosphosulfate 3'-phosphotransferase)(3'-phosphoadenosine-5'-phosphosulfate synthetase)]."; (812:) "Bifunctional 3'-phosphoadenosine 5'-phosphosulfate synthetase 2(PAPS synthetase 2) (PAPSS 2) (Sulfurylase kinase 2) (SK2) (SK 2)[Includes:) Sulfate adenylyltransferase (Sulfate adenylatetransferase) (SAT) (ATP-sulfurylase); Adenylyl-sulfate kinase(Adenylylsulfate 3'-phosphotransferase) (APS kinase)(Adenosine-5'-phosphosulfate 3'-phosphotransferase)(3'-phosphoadenosine-5'-phosphosulfate synthetase)]."; (813:) bifunctional ATP sulfurylase/adenosine 5'-phosphosulfate kinase[Homo sapiens]; (814:) "Bifunctional coenzyme A synthase (CoA synthase) (NBP) (POV-2)[Includes:) Phosphopantetheine adenylyltransferase(Pantetheine-phosphate adenylyltransferase) (PPAT) (Dephospho-CoApyrophosphorylase); Dephospho-CoA kinase (DPCK) (DephosphocoenzymeA kinase) (DPCOAK)]."; (815:) "Bifunctional heparan sulfate N-deacetylase/N-sulfotransferase 1(Glucosaminyl N-deacetylase/N-sulfotransferase 1) (NDST-1)([Heparan sulfate]-glucosamine N-sulfotransferase 1) (HSNST 1)(N-heparan sulfate sulfotransferase 1) (N-HSST 1) [Includes:Heparan sulfate N-deacetylase 1 ; Heparan sulfateN-sulfotransferase 1]."; (816:) "Bifunctional heparan sulfate N-deacetylase/N-sulfotransferase 2(Glucosaminyl N-deacetylase/N-

sulfotransferase 2) (NDST-2)(N-heparan sulfate sulfotransferase 2) (N-HSST 2) [Includes:Heparan sulfate N-deacetylase 2 ; Heparan sulfateN-sulfotransferase 2]."; (817:) "Bifunctional heparan sulfate N-deacetylase/N-sulfotransferase 3(Glucosaminyl N-deacetylase/N-sulfotransferase 3) (NDST-3)(hNDST-3) (N-heparan sulfate sulfotransferase 3) (N-HSST 3)[Includes:) Heparan sulfate N-deacetylase 3 ; Heparan sulfateN-sulfotransferase 3]."; (818:) "Bifunctional heparan sulfate N-deacetylase/N-sulfotransferase 4(Glucosaminyl N-deacetylase/N-sulfotransferase 4) (NDST-4)(N-heparan sulfate sulfotransferase 4) (N-HSST 4) [Includes:Heparan sulfate N-deacetylase 4 ; Heparan sulfateN-sulfotransferase 4]."; (819:) "Bifunctional methylenetetrahydrofolatedehydrogenase/cyclohydrolase, mitochondrial precursor [Includes:NAD-dependent methylenetetrahydrofolate dehydrogenase ;Methenyltetrahydrofolate cyclohydrolase]."; (820:) bifunctional phosphopantetheine adenylyl transferase / dephosphoCoA kinase [Homo sapiens]; (821:) "Bifunctional protein NCOAT (Nuclear cytoplasmic O-GlcNAcase andacetyltransferase) (Meningioma-expressed antigen 5) [Includes:Beta-hexosaminidase (N-acetyl-beta-glucosaminidase)(Beta-N-acetylhexosaminidase) (Hexosaminidase C)(N-acetyl-beta-D-glucosaminidase) (O-GlcNAcase); Histoneacetyltransferase (HAT)]."; (822:) "Bifunctional UDP-N-acetylglucosamine2-epimerase/N-acetylmannosamine kinase(UDP-GlcNAc-2-epimerase/ManAc kinase) [Includes:UDP-N-acetylglucosamine 2-epimerase (Uridinediphosphate-N-acetylglucosamine-2-epimerase)(UDP-GlcNAc-2-epimerase); N-acetylmannosamine kinase (ManAckinase)]."; (823:) bile acid beta-glucosidase [Homo sapiens]; (824:) bile acid CoA:) Amino acid N-acyltransferase; (825:) Bile acid CoA:amino acid N-acyltransferase (BAT) (BACAT) (GlycineN-choloyltransferase) (Long-chain fatty-acyl-CoA hydrolase); (826:) bile acid Coenzyme A:) amino acid N-acyltransferase [Homo sapiens]; (827:) Bile acid receptor (Farnesoid X-activated receptor) (Farnesolreceptor HRR-1) (Retinoid X receptor-interacting protein 14)(RXR-interacting protein 14); (828:) Bile acyl-CoA synthetase (BACS) (Bile acid CoA ligase) (BA-CoAligase) (BAL) (Cholate--CoA ligase) (Very long-chain acyl-CoAsynthetase homolog 2) (VLCSH2) (VLCS-H2) (Very long chain acyl-CoAsynthetase-related protein) (VLACS-related) (VLACSR)(Fatty-acid-coenzyme A ligase, very long-chain 3) (Fatty acidtransport protein 5) (FATP-5) (Solute carrier family 27 member 5); (829:) Bile salt sulfotransferase (Hydroxysteroid Sulfotransferase) (HST)(Dehydroepiandrosterone sulfotransferase) (DHEA-ST) (ST2) (ST2A3); (830:) Bile salt-activated lipase precursor (BAL) (Bile salt-stimulatedlipase) (BSSL) (Carboxyl ester lipase) (Sterol esterase)(Cholesterol

esterase) (Pancreatic lysophospholipase); (831:) biliverdin reductase B (flavin reductase (NADPH)) [Homo sapiens]; (832:) biphenyl hydrolase-like [Homo sapiens]; (833:) Bis(5'-adenosyl)-triphosphatase (Diadenosine5',5'''-P1,P3-triphosphate hydrolase) (Dinucleosidetriphosphatase)(AP3A hydrolase) (AP3AASE) (Fragile histidine triad protein); (834:) BK158_1 (OTTHUMP00000040718) variant [Homo sapiens]; (835:) BK158_1 [Homo sapiens]; (836:) bleomycin hydrolase [Homo sapiens]; (837:) Blue-sensitive opsin (BOP) (Blue cone photoreceptor pigment); (838:) Bombesin receptor subtype-3 (BRS-3); (839:) bone morphogenetic protein 1 isoform 1, precursor [Homo sapiens]; (840:) bone morphogenetic protein 1 isoform 2, precursor [Homo sapiens]; (841:) bone morphogenetic protein 1 isoform 3, precursor [Homo sapiens]; (842:) Bone morphogenetic protein 1 precursor (BMP-1) (ProcollagenC-proteinase) (PCP) (Mammalian tolloid protein) (mTld); (843:) Bone morphogenetic protein receptor type IA precursor(Serine/threonine-protein kinase receptor R5) (SKR5) (Activinreceptor-like kinase 3) (ALK-3) (CD292 antigen); (844:) Bone morphogenetic protein receptor type IB precursor (CDw293antigen); (845:) Bone morphogenetic protein receptor type-2 precursor (Bonemorphogenetic protein receptor type II) (BMP type II receptor)(BMPR-II); (846:) bradykinin receptor B1 [Homo sapiens]; (847:) bradykinin receptor B2 [Homo sapiens]; (848:) brain creatine kinase [Homo sapiens]; (849:) brain glycogen phosphorylase [Homo sapiens]; (850:) brain-derived neurotrophic factor isoform a preproprotein [Homosapiens]; (851:) brain-derived neurotrophic factor isoform b preproprotein [Homosapiens]; (852:) brain-derived neurotrophic factor isoform c preproprotein [Homosapiens]; (853:) Brain-specific angiogenesis inhibitor 1 precursor; (854:) Brain-specific angiogenesis inhibitor 2 precursor; (855:) Brain-specific angiogenesis inhibitor 3 precursor; (856:) branched chain acyltransferase precursor; (857:) branched chain aminotransferase 1, cytosolic [Homo sapiens]; (858:) branched chain aminotransferase 2, mitochondrial [Homo sapiens]; (859:) branched chain keto acid dehydrogenase E1, alpha polypeptide [Homosapiens]; (860:) branching-enzyme interacting dual-specificity protein phosphataseBEDP [Homo sapiens]; (861:) Breast cancer type 1 susceptibility protein (RING finger protein53); (862:) Brefeldin A-inhibited guanine nucleotide-exchange protein 1(Brefeldin A-inhibited GEP 1) (p200 ARF-GEP1) (p200 ARF guaninenucleotide exchange factor); (863:) Brefeldin A-inhibited guanine nucleotide-exchange protein 2(Brefeldin A-inhibited GEP 2); (864:) bubblegum related protein [Homo sapiens]; (865:) butyrylcholinesterase precursor [Homo sapiens]; (866:) C->U-editing enzyme APOBEC-1 (Apolipoprotein B mRNA-editing enzyme1) (HEPR); (867:) C1 esterase inhibitor [Homo sapiens]; (868:) C10orf129

protein [Homo sapiens]; (869:) C1GALT1-specific chaperone 1 [Homo sapiens]; (870:) C1-tetrahydrofolate synthase [Homo sapiens]; (871:) "C-1-tetrahydrofolate synthase, cytoplasmic (C1-THF synthase)[Includes:) Methylenetetrahydrofolate dehydrogenase ;Methenyltetrahydrofolate cyclohydrolase ; Formyltetrahydrofolatesynthetase]."; (872:) C3a anaphylatoxin chemotactic receptor (C3a-R) (C3AR); (873:) C5a anaphylatoxin chemotactic receptor (C5a-R) (C5aR) (CD88antigen); (874:) C5a anaphylatoxin chemotactic receptor C5L2 (G-protein coupledreceptor 77); (875:) C9orf3 protein [Homo sapiens]; (876:) C9orf95 protein [Homo sapiens]; (877:) Ca2+/calmodulin-dependent protein kinase (EC 2.7.1.123) II gammachain, splice form B - human; (878:) Ca2+/calmodulin-dependent protein kinase kinase beta-3 [Homosapiens]; (879:) CAD protein [Homo sapiens]; (880:) cadherin 1, type 1 preproprotein [Homo sapiens]; (881:) Cadherin EGF LAG seven-pass G-type receptor 1 precursor (Flamingohomolog 2) (hFmi2); (882:) Cadherin EGF LAG seven-pass G-type receptor 2 precursor (Epidermalgrowth factor-like 2) (Multiple epidermal growth factor-likedomains 3) (Flamingo 1); (883:) Cadherin EGF LAG seven-pass G-type receptor 3 precursor (Flamingohomolog 1) (hFmi1) (Multiple epidermal growth factor-like domains2) (Epidermal growth factor-like 1); (884:) Calcitonin gene-related peptide type 1 receptor precursor (CGRPtype 1 receptor) (Calcitonin receptor-like receptor); (885:) calcitonin gene-related peptide-receptor component protein isoform a [Homo sapiens]; (886:) calcitonin gene-related peptide-receptor component protein isoform b [Homo sapiens]; (887:) calcitonin gene-related peptide-receptor component protein isoform c [Homo sapiens]; (888:) Calcitonin receptor precursor (CT-R); (889:) calcium activated nucleotidase 1 [Homo sapiens]; (890:) calcium receptor (clone phPCaR-4.0) - human; (891:) calcium receptor (clone phPCaR-5.2) - human; (892:) Calcium/calmodulin-dependent 3',5'-cyclic nucleotidephosphodiesterase 1A (Cam-PDE 1A) (61 kDa Cam-PDE) (hCam-1); (893:) Calcium/calmodulin-dependent 3',5'-cyclic nucleotidephosphodiesterase 1B (Cam-PDE 1B) (63 kDa Cam-PDE); (894:) Calcium/calmodulin-dependent 3',5'-cyclic nucleotidephosphodiesterase 1C (Cam-PDE 1C) (hCam-3); (895:) calcium/calmodulin-dependent protein kinase I [Homo sapiens]; (896:) calcium/calmodulin-dependent protein kinase II delta isoform 1[Homo sapiens]; (897:) calcium/calmodulin-dependent protein kinase II delta isoform 2[Homo sapiens]; (898:) calcium/calmodulin-dependent protein kinase II delta isoform 3[Homo sapiens]; (899:) calcium/calmodulin-dependent protein kinase II gamma isoform 1[Homo sapiens]; (900:) calcium/calmodulin-dependent protein kinase II gamma isoform 2[Homo sapiens]; (901:) calcium/calmodulin-dependent protein

kinase II gamma isoform 3[Homo sapiens]; (902:) calcium/calmodulin-dependent protein kinase II gamma isoform 4[Homo sapiens]; (903:) calcium/calmodulin-dependent protein kinase II gamma isoform 5[Homo sapiens]; (904:) calcium/calmodulin-dependent protein kinase II gamma isoform 6[Homo sapiens]; (905:) calcium/calmodulin-dependent protein kinase IIA isoform 1 [Homosapiens]; (906:) calcium/calmodulin-dependent protein kinase IIA isoform 2 [Homosapiens]; (907:) calcium/calmodulin-dependent protein kinase IIB isoform 1 [Homosapiens]; (908:) calcium/calmodulin-dependent protein kinase IIB isoform 2 [Homosapiens]; (909:) calcium/calmodulin-dependent protein kinase IIB isoform 3 [Homosapiens]; (910:) calcium/calmodulin-dependent protein kinase IIB isoform 4 [Homosapiens]; (911:) calcium/calmodulin-dependent protein kinase IIB isoform 5 [Homosapiens]; (912:) calcium/calmodulin-dependent protein kinase IIB isoform 6 [Homosapiens]; (913:) calcium/calmodulin-dependent protein kinase IIB isoform 7 [Homosapiens]; (914:) calcium/calmodulin-dependent protein kinase IIB isoform 8 [Homosapiens]; (915:) calcium/calmodulin-dependent protein kinase IV [Homo sapiens]; (916:) Calcium/calmodulin-dependent protein kinase kinase 1(Calcium/calmodulin-dependent protein kinase kinase alpha)(CaM-kinase kinase alpha) (CaM-KK alpha) (CaMKK alpha) (CaMKK 1)(CaM-kinase IV kinase); (917:) Calcium/calmodulin-dependent protein kinase kinase 2(Calcium/calmodulin-dependent protein kinase kinase beta)(CaM-kinase kinase beta) (CaM-KK beta) (CaMKK beta); (918:) Calcium/calmodulin-dependent protein kinase type 1 (CaM kinase I)(CaM-KI) (CaM kinase I alpha) (CaMKI-alpha); (919:) Calcium/calmodulin-dependent protein kinase type 1B (CaM kinase IB)(CaM kinase I beta) (CaMKI-beta) (CaM-KI beta) (Pregnancyup-regulated non-ubiquitously expressed CaM kinase); (920:) Calcium/calmodulin-dependent protein kinase type 1D (CaM kinase ID)(CaM kinase I delta) (CaMKI-delta) (CaM-KI delta) (CaMKI delta)(Camk1D) (CamKI-like protein kinase) (CKLiK); (921:) Calcium/calmodulin-dependent protein kinase type 1G (CaM kinase IG)(CaM kinase I gamma) (CaMKI gamma) (CaMKI-gamma) (CaM-KI gamma)(CaMKIG) (CaMK-like CREB kinase III) (CLICK III); (922:) Calcium/calmodulin-dependent protein kinase type II alpha chain(CaM-kinase II alpha chain) (CaM kinase II alpha subunit) (CaMK-IIsubunit alpha); (923:) Calcium/calmodulin-dependent protein kinase type II beta chain(CaM-kinase II beta chain) (CaM kinase II subunit beta) (CaMK-IIsubunit beta); (924:) Calcium/calmodulin-dependent protein kinase type II delta chain(CaM-kinase II delta chain) (CaM kinase II subunit delta) (CaMK-IIsubunit delta); (925:) Calcium/calmodulin-dependent protein kinase type II gamma chain(CaM-kinase II

gamma chain) (CaM kinase II gamma subunit) (CaMK-IIsubunit gamma); (926:) Calcium/calmodulin-dependent protein kinase type IV (CAM kinase-GR)(CaMK IV); (927:) Calcium-dependent phospholipase A2 precursor (Phosphatidylcholine2-acylhydrolase) (PLA2-10) (Group V phospholipase A2); (928:) calcium-independent phospholipase A2 [Homo sapiens]; (929:) calcium-sensing receptor [Homo sapiens]; (930:) calcium-transporting ATPase 2C1 isoform 1a [Homo sapiens]; (931:) calcium-transporting ATPase 2C1 isoform 1b [Homo sapiens]; (932:) calcium-transporting ATPase 2C1 isoform 1c [Homo sapiens]; (933:) calcium-transporting ATPase 2C1 isoform 1d [Homo sapiens]; (934:) Calcium-transporting ATPase type 2C member 1 (ATPase 2C1)(ATP-dependent Ca(2+) pump PMR1); (935:) Calmodulin (Vertebrate); (936:) calmodulin-like skin protein [Homo sapiens]; (937:) calnexin precursor [Homo sapiens]; (938:) calpain [Homo sapiens]; (939:) calpain 1, large subunit [Homo sapiens]; (940:) calpain 2, large subunit [Homo sapiens]; (941:) calpain 3 isoform a [Homo sapiens]; (942:) calpain 3 isoform b [Homo sapiens]; (943:) calpain 3 isoform c [Homo sapiens]; (944:) calpain 3 isoform d [Homo sapiens]; (945:) calpain 3 isoform e [Homo sapiens]; (946:) calpain 3 isoform f [Homo sapiens]; (947:) calpain 3 isoform g [Homo sapiens]; (948:) calpain 3 isoform h [Homo sapiens]; (949:) Calpain-1 catalytic subunit (Calpain-1 large subunit)(Calcium-activated neutral proteinase 1) (CANP 1) (Calpain mu-type)(muCANP) (Micromolar-calpain); (950:) Calpain-2 catalytic subunit precursor (Calpain-2 large subunit)(Calcium-activated neutral proteinase 2) (CANP 2) (Calpain M-type)(M-calpain) (Millimolar-calpain) (Calpain large polypeptide L2); (951:) Calpain-3 (Calpain L3) (Calpain p94) (Calcium-activated neutralproteinase 3) (CANP 3) (Muscle-specific calcium-activated neutralprotease 3) (nCL-1); (952:) C-alpha-formyglycine-generating enzyme [Homo sapiens]; (953:) cAMP and cAMP-inhibited cGMP 3',5'-cyclic phosphodiesterase 10A; (954:) cAMP responsive element binding protein 3 [Homo sapiens]; (955:) cAMP-dependent protein kinase catalytic subunit alpha isoform 1[Homo sapiens]; (956:) cAMP-dependent protein kinase catalytic subunit alpha isoform 2[Homo sapiens]; (957:) cAMP-dependent protein kinase inhibitor alpha (PKI-alpha)(cAMP-dependent protein kinase inhibitor, muscle/brain isoform); (958:) cAMP-dependent protein kinase inhibitor beta (PKI-beta); (959:) cAMP-dependent protein kinase inhibitor gamma (PKI-gamma); (960:) cAMP-dependent protein kinase type I-alpha regulatory subunit(Tissue-specific extinguisher 1) (TSE1); (961:) cAMP-dependent protein kinase type I-beta regulatory subunit; (962:) cAMP-dependent protein kinase type II-alpha regulatory subunit; (963:) cAMP-dependent protein kinase type II-beta regulatory subunit;

(964:) cAMP-dependent protein kinase, alpha-catalytic subunit (PKAC-alpha); (965:) cAMP-dependent protein kinase, beta-catalytic subunit (PKA C-beta); (966:) cAMP-dependent protein kinase, gamma-catalytic subunit (PKAC-gamma); (967:) cAMP-specific 3',5'-cyclic phosphodiesterase 4A (DPDE2) (PDE46); (968:) cAMP-specific 3',5'-cyclic phosphodiesterase 4B (DPDE4) (PDE32); (969:) cAMP-specific 3',5'-cyclic phosphodiesterase 4C (DPDE1) (PDE21); (970:) cAMP-specific 3',5'-cyclic phosphodiesterase 4D (DPDE3) (PDE43); (971:) cAMP-specific 3',5'-cyclic phosphodiesterase 7B; (972:) cAMP-specific phosphodiesterase 4D [Homo sapiens]; (973:) Cannabinoid receptor 1 (CB1) (CB-R) (CANN6); (974:) Cannabinoid receptor 2 (CB2) (CB-2) (CX5); (975:) CAP10-like 46 kDa protein precursor (Myelodysplastic syndromesrelative protein); (976:) capping enzyme 1 [Homo sapiens]; (977:) capping enzyme 1A [Homo sapiens]; (978:) capping enzyme 1B [Homo sapiens]; (979:) Carbamoyl-phosphate synthase [ammonia], mitochondrial precursor(Carbamoyl-phosphate synthetase I) (CPSase I); (980:) carbamoyl-phosphate synthetase 1, mitochondrial [Homo sapiens]; (981:) Carbamoyl-phosphate synthetase 2, aspartate transcarbamylase, anddihydroorotase [Homo sapiens]; (982:) carbamoylphosphate synthetase 2/aspartatetranscarbamylase/dihydroorotase [Homo sapiens]; (983:) carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 6 [Homosapiens]; (984:) carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 7 [Homosapiens]; (985:) carbohydrate (N-acetylglucosamine-6-O) sulfotransferase 2 [Homosapiens]; (986:) Carbohydrate sulfotransferase 10 (HNK-1 sulfotransferase) (HNK1ST)(HNK-1ST) (huHNK-1ST); (987:) Carbohydrate sulfotransferase 11 (Chondroitin 4-O-sulfotransferase1) (Chondroitin 4-sulfotransferase 1) (C4ST) (C4ST-1) (C4S-1); (988:) Carbohydrate sulfotransferase 12 (Chondroitin 4-O-sulfotransferase2) (Chondroitin 4-sulfotransferase 2) (C4ST2) (C4ST-2)(Sulfotransferase Hlo); (989:) Carbohydrate sulfotransferase 13 (Chondroitin 4-O-sulfotransferase3) (Chondroitin 4-sulfotransferase 3) (C4ST3) (C4ST-3); (990:) Carbohydrate sulfotransferase 2 (N-acetylglucosamine6-O-sulfotransferase 1) (GlcNAc6ST-1) (Gn6ST)(Galactose/N-acetylglucosamine/N-acetylglucosamine6-O-sulfotransferase 2) (GST-2); (991:) Carbohydrate sulfotransferase 3 (Chondroitin 6-sulfotransferase)(Chondroitin 6-O-sulfotransferase 1) (C6ST-1) (C6ST)(Galactose/N-acetylglucosamine/N-acetylglucosamine6-O-sulfotransferase 0) (GST-0); (992:) Carbohydrate sulfotransferase 4 (N-acetylglucosamine6-O-sulfotransferase 2) (GlcNAc6ST-2) (High endothelial cellsN-acetylglucosamine 6-O-sulfotransferase) (HEC-GlcNAc6ST)(L-selectin ligand sulfotransferase) (LSST)(Galactose/N-

acetylglucosamine/N-acetylglucosamine6-O-sulfotransferase 3) (GST-3); (993:) Carbohydrate sulfotransferase 7 (Chondroitin 6-sulfotransferase 2)(C6ST-2) (N-acetylglucosamine 6-O-sulfotransferase 1) (GlcNAc6ST-4)(Galactose/N-acetylglucosamine/N-acetylglucosamine6-O-sulfotransferase 5) (GST-5); (994:) Carbohydrate sulfotransferase 8(N-acetylgalactosamine-4-O-sulfotransferase 1)(GalNAc-4-O-sulfotransferase 1) (GalNAc-4-ST1) (GalNAc4ST-1); (995:) Carbohydrate sulfotransferase 9(N-acetylgalactosamine-4-O-sulfotransferase 2)(GalNAc-4-O-sulfotransferase 2) (GalNAc-4-ST2); (996:) Carbohydrate sulfotransferase D4ST1 (Dermatan 4-sulfotransferase 1)(D4ST-1) (hD4ST); (997:) Carbonic anhydrase 12 precursor (Carbonic anhydrase XII) (Carbonatedehydratase XII) (CA-XII) (Tumor antigen HOM-RCC-3.1.3); (998:) Carbonic anhydrase 4 precursor (Carbonic anhydrase IV) (Carbonatedehydratase IV) (CA-IV); (999:) Carbonic Anhydrase I (E.C.4.2.1.1) Complexed With Bicarbonate; (1000:) carbonic anhydrase I [Homo sapiens]; (1001:) carbonic anhydrase II [Homo sapiens]; (1002:) carbonic anhydrase IV precursor [Homo sapiens]; (1003:) carbonic anhydrase IX precursor [Homo sapiens]; (1004:) carbonic anhydrase VIII [Homo sapiens]; (1005:) carbonyl reductase 1 [Homo sapiens]; (1006:) carbonyl reductase 3 [Homo sapiens]; (1007:) carboxyl ester lipase precursor [Homo sapiens]; (1008:) carboxylesterase 1 isoform a precursor [Homo sapiens]; (1009:) carboxylesterase 1 isoform b precursor [Homo sapiens]; (1010:) carboxylesterase 1 isoform c precursor [Homo sapiens]; (1011:) carboxylesterase 2 isoform 1 [Homo sapiens]; (1012:) carboxylesterase 2 isoform 2 [Homo sapiens]; (1013:) carboxylesterase; (1014:) carboxypeptidase A2 (pancreatic) [Homo sapiens]; (1015:) carboxypeptidase A4 preproprotein [Homo sapiens]; (1016:) carboxypeptidase A5 [Homo sapiens]; (1017:) carboxypeptidase B precursor [Homo sapiens]; (1018:) Carboxypeptidase D precursor (Metallocarboxypeptidase D) (gp180); (1019:) carboxypeptidase E precursor [Homo sapiens]; (1020:) Carboxypeptidase M precursor (CPM); (1021:) carboxypeptidase N, polypeptide 1, 50kD precursor [Homo sapiens]; (1022:) carboxypeptidase Z isoform 1 [Homo sapiens]; (1023:) carboxypeptidase Z isoform 2 precursor [Homo sapiens]; (1024:) carboxypeptidase Z isoform 3 [Homo sapiens]; (1025:) Carboxypeptidase Z precursor (CPZ); (1026:) carnitine acetyltransferase isoform 1 precursor [Homo sapiens]; (1027:) carnitine acetyltransferase isoform 2 [Homo sapiens]; (1028:) carnitine acetyltransferase isoform 3 precursor [Homo sapiens]; (1029:) Carnitine O-acetyltransferase (Carnitine acetylase) (CAT)(Carnitine acetyltransferase) (CrAT); (1030:) carnitine O-octanoyltransferase [Homo sapiens]; (1031:) Carnitine O-palmitoyltransferase I, liver isoform (CPT I) (CPTI-L)(Carnitine

palmitoyltransferase 1A); (1032:) carnitine palmitoyltransferase 1A isoform 1 [Homo sapiens]; (1033:) carnitine palmitoyltransferase 1A isoform 2 [Homo sapiens]; (1034:) carnitine palmitoyltransferase 1B isoform a [Homo sapiens]; (1035:) carnitine palmitoyltransferase 1B isoform b [Homo sapiens]; (1036:) "Cartilage intermediate layer protein 1 precursor (CILP-1)(Cartilage intermediate-layer protein) [Contains:) Cartilageintermediate layer protein 1 C1; Cartilage intermediate layerprotein 1 C2]."; (1037:) Cas-Br-M (murine) ecotropic retroviral transforming sequence [Homosapiens]; (1038:) casein alpha s1 isoform 1 [Homo sapiens]; (1039:) casein alpha s1 isoform 2 [Homo sapiens]; (1040:) casein beta [Homo sapiens]; (1041:) casein kinase 1, gamma 1 [Homo sapiens]; (1042:) casein kinase 1, gamma 1 isoform L [Homo sapiens]; (1043:) casein kinase 2, alpha prime polypeptide [Homo sapiens]; (1044:) casein kinase 2, beta polypeptide [Homo sapiens]; (1045:) Casein kinase I isoform delta (CKI-delta) (CKId); (1046:) casein kinase II alpha 1 subunit isoform a [Homo sapiens]; (1047:) casein kinase II alpha 1 subunit isoform b [Homo sapiens]; (1048:) CASH alpha protein [Homo sapiens]; (1049:) CASP1 protein [Homo sapiens]; (1050:) CASP10 protein [Homo sapiens]; (1051:) CASP12P1 [Homo sapiens]; (1052:) CASP2 [Homo sapiens]; (1053:) CASP8 and FADD-like apoptosis regulator [Homo sapiens]; (1054:) "CASP8 and FADD-like apoptosis regulator precursor (CellularFLICE-like inhibitory protein) (c-FLIP) (Caspase-eight-relatedprotein) (Casper) (Caspase-like apoptosis regulatory protein)(CLARP) (MACH-related inducer of toxicity) (MRIT) (Caspase homolog)(CASH) (Inhibitor of FLICE) (I-FLICE) (FADD-like antiapoptoticmolecule 1) (FLAME-1) (Usurpin) [Contains:) CASP8 and FADD-likeapoptosis regulator subunit p43; CASP8 and FADD-like apoptosisregulator subunit p12]."; (1055:) CASP8 protein [Homo sapiens]; (1056:) caspase 1 isoform alpha precursor [Homo sapiens]; (1057:) caspase 1 isoform alpha precursor variant [Homo sapiens]; (1058:) caspase 1 isoform beta precursor [Homo sapiens]; (1059:) caspase 1 isoform delta [Homo sapiens]; (1060:) caspase 1 isoform epsilon [Homo sapiens]; (1061:) caspase 1 isoform gamma precursor [Homo sapiens]; (1062:) Caspase 1, apoptosis-related cysteine peptidase (interleukin 1,beta, convertase) [Homo sapiens]; (1063:) caspase 10 [Homo sapiens]; (1064:) caspase 10 isoform a preproprotein [Homo sapiens]; (1065:) caspase 10 isoform b preproprotein [Homo sapiens]; (1066:) caspase 10 isoform d preproprotein [Homo sapiens]; (1067:) caspase 10, apoptosis-related cysteine peptidase [Homo sapiens]; (1068:) caspase 14 precursor [Homo sapiens]; (1069:) Caspase 14, apoptosis-related cysteine peptidase [Homo sapiens]; (1070:) caspase 2 isoform 1 preproprotein [Homo sapiens]; (1071:) caspase 2 isoform 2

precursor variant [Homo sapiens]; (1072:) caspase 2 isoform 3 [Homo sapiens]; (1073:) Caspase 2, apoptosis-related cysteine peptidase (neural precursorcell expressed, developmentally down-regulated 2) [Homo sapiens]; (1074:) caspase 2, apoptosis-related cysteine protease (neural precursorcell expressed, developmentally down-regulated 2) [Homo sapiens]; (1075:) caspase 3 preproprotein [Homo sapiens]; (1076:) Caspase 3, apoptosis-related cysteine peptidase [Homo sapiens]; (1077:) caspase 3, apoptosis-related cysteine protease [Homo sapiens]; (1078:) caspase 4 isoform alpha precursor [Homo sapiens]; (1079:) caspase 4 isoform delta [Homo sapiens]; (1080:) caspase 4 isoform gamma precursor [Homo sapiens]; (1081:) Caspase 4, apoptosis-related cysteine peptidase [Homo sapiens]; (1082:) caspase 5 precursor [Homo sapiens]; (1083:) Caspase 5, apoptosis-related cysteine peptidase [Homo sapiens]; (1084:) caspase 6 isoform alpha preproprotein [Homo sapiens]; (1085:) caspase 6 isoform beta [Homo sapiens]; (1086:) Caspase 6, apoptosis-related cysteine peptidase [Homo sapiens]; (1087:) caspase 6, apoptosis-related cysteine protease [Homo sapiens]; (1088:) caspase 7 isoform alpha [Homo sapiens]; (1089:) caspase 7 isoform alpha precursor [Homo sapiens]; (1090:) caspase 7 isoform beta [Homo sapiens]; (1091:) caspase 7 isoform delta [Homo sapiens]; (1092:) Caspase 7, apoptosis-related cysteine peptidase [Homo sapiens]; (1093:) caspase 7, apoptosis-related cysteine protease [Homo sapiens]; (1094:) caspase 8 isoform A [Homo sapiens]; (1095:) caspase 8 isoform B precursor [Homo sapiens]; (1096:) caspase 8 isoform C [Homo sapiens]; (1097:) caspase 8 isoform E [Homo sapiens]; (1098:) caspase 8, apoptosis-related cysteine peptidase [Homo sapiens]; (1099:) caspase 9 isoform alpha preproprotein [Homo sapiens]; (1100:) caspase 9 isoform alpha preproprotein variant [Homo sapiens]; (1101:) caspase 9 isoform beta preproprotein [Homo sapiens]; (1102:) caspase 9 short isoform [Homo sapiens]; (1103:) Caspase 9, apoptosis-related cysteine peptidase [Homo sapiens]; (1104:) caspase 9, apoptosis-related cysteine protease [Homo sapiens]; (1105:) caspase-1 dominant-negative inhibitor pseudo-ICE isoform 1 [Homosapiens]; (1106:) caspase-1 dominant-negative inhibitor pseudo-ICE isoform 2 [Homosapiens]; (1107:) caspase-1 isoform zeta precursor [Homo sapiens]; (1108:) "Caspase-1 precursor (CASP-1) (Interleukin-1 beta convertase)(IL-1BC) (IL-1 beta-converting enzyme) (ICE) (Interleukin-1beta-converting enzyme) (p45) [Contains:) Caspase-1 p20 subunit;Caspase-1 p10 subunit]."; (1109:) "Caspase-10 precursor (CASP-10) (ICE-like apoptotic protease 4)(Apoptotic protease Mch-4) (FAS-associated death domain proteininterleukin-1B-converting enzyme 2) (FLICE2) [Contains:) Caspase-

10subunit p23/17; Caspase-10 subunit p12]."; (1110:) caspase-10/d [Homo sapiens]; (1111:) caspase-10a [Homo sapiens]; (1112:) caspase-10b [Homo sapiens]; (1113:) "Caspase-14 precursor (CASP-14) [Contains:) Caspase-14 subunit 1;Caspase-14 subunit 2]."; (1114:) "Caspase-2 precursor (CASP-2) (ICH-1 protease) (ICH-1L/1S)[Contains:) Caspase-2 subunit p18; Caspase-2 subunit p13; Caspase-2subunit p12]."; (1115:) caspase-3 [Homo sapiens]; (1116:) "Caspase-3 precursor (CASP-3) (Apopain) (Cysteine protease CPP32)(Yama protein) (CPP-32) (SREBP cleavage activity 1) (SCA-1)[Contains:) Caspase-3 p17 subunit; Caspase-3 p12 subunit]."; (1117:) "Caspase-4 precursor (CASP-4) (ICH-2 protease) (TX protease)(ICE(rel)-II) [Contains:) Caspase-4 subunit 1; Caspase-4 subunit 2]."; (1118:) "Caspase-5 precursor (CASP-5) (ICH-3 protease) (TY protease)(ICE(rel)-III) [Contains:) Caspase-5 subunit p20; Caspase-5 subunitp10]."; (1119:) caspase-5/b [Homo sapiens]; (1120:) caspase-5/f [Homo sapiens]; (1121:) "Caspase-6 precursor (CASP-6) (Apoptotic protease Mch-2) [Contains:Caspase-6 subunit p18; Caspase-6 subunit p11]."; (1122:) "Caspase-7 precursor (CASP-7) (ICE-like apoptotic protease 3)(ICE-LAP3) (Apoptotic protease Mch-3) (CMH-1) [Contains:) Caspase-7subunit p20; Caspase-7 subunit p11]."; (1123:) caspase-8 [Homo sapiens]; (1124:) "Caspase-8 precursor (CASP-8) (ICE-like apoptotic protease 5)(MORT1-associated CED-3 homolog) (MACH) (FADD-homologousICE/CED-3-like protease) (FADD-like ICE) (FLICE) (Apoptoticcysteine protease) (Apoptotic protease Mch-5) (CAP4) [Contains:Caspase-8 subunit p18; Caspase-8 subunit p10]."; (1125:) caspase-8L [Homo sapiens]; (1126:) Caspase-9 [Homo sapiens]; (1127:) caspase-9 beta [Homo sapiens]; (1128:) "Caspase-9 precursor (CASP-9) (ICE-like apoptotic protease 6)(ICE-LAP6) (Apoptotic protease Mch-6) (Apoptoticprotease-activating factor 3) (APAF-3) [Contains:) Caspase-9 subunitp35; Caspase-9 subunit p10]."; (1129:) caspase-9S precursor [Homo sapiens]; (1130:) caspase-like apoptosis regulatory protein [Homo sapiens]; (1131:) Casper [Homo sapiens]; (1132:) catalase [Homo sapiens]; (1133:) Catechol O-methyltransferase; (1134:) catechol-O-methyltransferase isoform MB-COMT [Homo sapiens]; (1135:) catechol-O-methyltransferase isoform S-COMT [Homo sapiens]; (1136:) catenin (cadherin-associated protein), beta 1, 88kDa [Homosapiens]; (1137:) cathepsin B preproprotein [Homo sapiens]; (1138:) cathepsin C isoform a preproprotein [Homo sapiens]; (1139:) cathepsin C isoform b precursor [Homo sapiens]; (1140:) cathepsin D preproprotein [Homo sapiens]; (1141:) Cathepsin E precursor; (1142:) Cathepsin F precursor (CATSF); (1143:) cathepsin G preproprotein [Homo sapiens]; (1144:) cathepsin H isoform a preproprotein [Homo sapiens]; (1145:) cathepsin H

isoform b precursor [Homo sapiens]; (1146:) cathepsin K preproprotein [Homo sapiens]; (1147:) cathepsin L preproprotein [Homo sapiens]; (1148:) Cathepsin L2 precursor (Cathepsin V) (Cathepsin U); (1149:) cathepsin O [Homo sapiens]; (1150:) Cathepsin O precursor; (1151:) cathepsin O preproprotein [Homo sapiens]; (1152:) cathepsin S [Homo sapiens]; (1153:) cathepsin S preproprotein [Homo sapiens]; (1154:) Cation-dependent mannose-6-phosphate receptor precursor (CD Man-6-Preceptor) (CD-MPR) (46 kDa mannose 6-phosphate receptor) (MPR 46); (1155:) cation-dependent mannose-6-phosphate receptor precursor [Homosapiens]; (1156:) Cation-independent mannose-6-phosphate receptor precursor (CIMan-6-P receptor) (CI-MPR) (M6PR) (Insulin-like growth factor 2receptor) (Insulin-like growth factor II receptor) (IGF-IIreceptor) (M6P/IGF2 receptor) (M6P/IGF2R) (300 kDa mannose6-phosphate receptor) (MPR 300) (MPR300) (CD222 antigen); (1157:) caveolin 1 [Homo sapiens]; (1158:) CBS protein [Homo sapiens]; (1159:) C-C chemokine receptor type 1 (C-C CKR-1) (CC-CKR-1) (CCR-1) (CCR1)(Macrophage inflammatory protein 1-alpha receptor) (MIP-1alpha-R)(RANTES-R) (HM145) (LD78 receptor) (CD191 antigen); (1160:) C-C chemokine receptor type 10 (C-C CKR-10) (CC-CKR-10) (CCR-10)(G-protein coupled receptor 2); (1161:) C-C chemokine receptor type 11 (C-C CKR-11) (CC-CKR-11) (CCR-11)(CC chemokine receptor-like 1) (CCRL1) (CCX CKR); (1162:) C-C chemokine receptor type 2 (C-C CKR-2) (CC-CKR-2) (CCR-2) (CCR2)(Monocyte chemoattractant protein 1 receptor) (MCP-1-R) (CD192antigen); (1163:) C-C chemokine receptor type 3 (C-C CKR-3) (CC-CKR-3) (CCR-3) (CCR3)(CKR3) (Eosinophil eotaxin receptor) (CD193 antigen); (1164:) C-C chemokine receptor type 4 (C-C CKR-4) (CC-CKR-4) (CCR-4) (CCR4)(K5-5); (1165:) C-C chemokine receptor type 5 (C-C CKR-5) (CC-CKR-5) (CCR-5) (CCR5)(HIV-1 fusion coreceptor) (CHEMR13) (CD195 antigen); (1166:) C-C chemokine receptor type 6 (C-C CKR-6) (CC-CKR-6) (CCR-6) (LARCreceptor) (GPR-CY4) (GPRCY4) (Chemokine receptor-like 3) (CKR-L3)(DRY6) (G-protein coupled receptor 29) (CD196 antigen); (1167:) C-C chemokine receptor type 7 precursor (C-C CKR-7) (CC-CKR-7)(CCR-7) (MIP-3 beta receptor) (EBV-induced G-protein coupledreceptor 1) (EBI1) (BLR2) (CD197 antigen) (CDw197); (1168:) C-C chemokine receptor type 8 (C-C CKR-8) (CC-CKR-8) (CCR-8)(GPR-CY6) (GPRCY6) (Chemokine receptor-like 1) (CKR-L1) (TER1)(CMKBRL2) (CC-chemokine receptor CHEMR1) (CDw198 antigen); (1169:) C-C chemokine receptor type 9 (C-C CKR-9) (CC-CKR-9) (CCR-9)(GPR-9-6) (G-protein coupled receptor 28) (CDw199 antigen); (1170:) C-C chemokine receptor-like 2 (Putative MCP-1 chemokine receptor)(Chemokine receptor CCR11) (Chemokine receptor X); (1171:)

CCR4-NOT transcription complex, subunit 4 isoform a [Homo sapiens]; (1172:) CCR4-NOT transcription complex, subunit 4 isoform b [Homo sapiens]; (1173:) CD160 antigen precursor (Natural killer cell receptor BY55); (1174:) CD180 antigen precursor (Lymphocyte antigen 64) (Radioprotective105 kDa protein); (1175:) CD200 antigen isoform a precursor [Homo sapiens]; (1176:) CD200 antigen isoform b [Homo sapiens]; (1177:) CD209 antigen (Dendritic cell-specific ICAM-3-grabbing nonintegrin1) (DC-SIGN1) (DC-SIGN) (C-type lectin domain family 4 member L); (1178:) CD226 antigen precursor (DNAX accessory molecule 1) (DNAM-1); (1179:) CD2-associated protein (Cas ligand with multiple SH3 domains)(Adapter protein CMS); (1180:) CD38 antigen [Homo sapiens]; (1181:) CD40 antigen isoform 1 precursor [Homo sapiens]; (1182:) CD40 antigen isoform 2 precursor [Homo sapiens]; (1183:) CD44 antigen precursor (Phagocytic glycoprotein I) (PGP-1)(HUTCH-I) (Extracellular matrix receptor-III) (ECMR-III) (GP90lymphocyte homing/adhesion receptor) (Hermes antigen) (Hyaluronatereceptor) (Heparan sulfate proteoglycan) (Epican) (CDw44); (1184:) CD53 antigen [Homo sapiens]; (1185:) CD63 antigen isoform A [Homo sapiens]; (1186:) CD63 antigen isoform B [Homo sapiens]; (1187:) CD97 antigen precursor (Leukocyte antigen CD97); (1188:) CDC16 homolog [Homo sapiens]; (1189:) CDC26 subunit of anaphase promoting complex [Homo sapiens]; (1190:) Cdc34 [Homo sapiens]; (1191:) Cdk5 and Abl enzyme substrate 1 [Homo sapiens]; (1192:) Cdk5 and Abl enzyme substrate 2 [Homo sapiens]; (1193:) CDK5 and ABL1 enzyme substrate 1 (Interactor with CDK3 1) (Ik3-1); (1194:) CDK5 and ABL1 enzyme substrate 2 (Interactor with CDK3 2) (Ik3-2); (1195:) CDP-diacylglycerol--inositol 3-phosphatidyltransferase(Phosphatidylinositol synthase) (PtdIns synthase) (PI synthase); (1196:) Cell division control protein 2 homolog (p34 protein kinase)(Cyclin-dependent kinase 1) (CDK1); (1197:) Cell division control protein 42 homolog precursor (G25KGTP-binding protein); (1198:) cell division cycle 2 protein isoform 1 [Homo sapiens]; (1199:) cell division cycle 2 protein isoform 2 [Homo sapiens]; (1200:) cell division cycle 2-like 1 (PITSLRE proteins) isoform 1 [Homosapiens]; (1201:) cell division cycle 2-like 1 (PITSLRE proteins) isoform 2 [Homosapiens]; (1202:) cell division cycle 2-like 1 (PITSLRE proteins) isoform 3 [Homosapiens]; (1203:) cell division cycle 2-like 1 (PITSLRE proteins) isoform 4 [Homosapiens]; (1204:) cell division cycle 2-like 1 (PITSLRE proteins) isoform 5 [Homosapiens]; (1205:) cell division cycle 2-like 1 (PITSLRE proteins) isoform 6 [Homosapiens]; (1206:) cell division cycle 2-like 1 (PITSLRE proteins) isoform 8 [Homosapiens]; (1207:) cell division cycle 2-like 1 (PITSLRE proteins) isoform 9

[Homosapiens]; (1208:) Cell division cycle 34 [Homo sapiens]; (1209:) Cell division cycle 34 homolog (S. cerevisiae) [Homo sapiens]; (1210:) cell division cycle protein 23 [Homo sapiens]; (1211:) cell division cycle protein 27 [Homo sapiens]; (1212:) Cell division protein kinase 2 (p33 protein kinase); (1213:) Cell division protein kinase 4 (Cyclin-dependent kinase 4)(PSK-J3); (1214:) Cell division protein kinase 7 (CDK-activating kinase) (CAK) (TFIIHbasal transcription factor complex kinase subunit) (39 kDa proteinkinase) (P39 Mo15) (STK1) (CAK1); (1215:) Cell surface glycoprotein OX2 receptor precursor (CD200 cellsurface glycoprotein receptor); (1216:) Centaurin-gamma 1 (ARF-GAP with GTP-binding protein-like, ankyrinrepeat and pleckstrin homology domains 2) (AGAP-2)(Phosphatidylinositol-3-kinase enhancer) (PIKE) (GTP-binding andGTPase-activating protein 2) (GGAP2); (1217:) Centaurin-gamma 2 (ARF-GAP with GTP-binding protein-like, ankyrinrepeat and pleckstrin homology domains 1) (AGAP-1) (GTP-binding andGTPase-activating protein 1) (GGAP1); (1218:) Centaurin-gamma 3 (ARF-GAP with GTP-binding protein-like, ankyrinrepeat and pleckstrin homology domains 3) (AGAP-3) (MR1-interactingprotein) (MRIP-1) (CRAM-associated GTPase) (CRAG); (1219:) CGI-02 protein [Homo sapiens]; (1220:) CGI-11 protein [Homo sapiens]; (1221:) CGI-76 protein [Homo sapiens]; (1222:) cGMP-dependent protein kinase 1, alpha isozyme (CGK 1 alpha)(cGKI-alpha); (1223:) cGMP-dependent protein kinase 1, beta isozyme (cGK 1 beta)(cGKI-beta); (1224:) cGMP-dependent protein kinase 2 (CGK 2) (cGKII) (Type IIcGMP-dependent protein kinase); (1225:) cGMP-inhibited 3',5'-cyclic phosphodiesterase A (CyclicGMP-inhibited phosphodiesterase A) (CGI-PDE A); (1226:) cGMP-inhibited 3',5'-cyclic phosphodiesterase B (CyclicGMP-inhibited phosphodiesterase B) (CGI-PDE B) (CGIPDE1) (CGIP1); (1227:) cGMP-specific 3',5'-cyclic phosphodiesterase (CGB-PDE)(cGMP-binding cGMP-specific phosphodiesterase); (1228:) CHCHD2 protein [Homo sapiens]; (1229:) CHCHD4 protein [Homo sapiens]; (1230:) chemokine (C-C motif) ligand 14 isoform 1 precursor [Homo sapiens]; (1231:) chemokine (C-C motif) ligand 14 isoform 2 precursor [Homo sapiens]; (1232:) chemokine (C-C motif) ligand 7 precursor [Homo sapiens]; (1233:) chemokine (C-C motif) receptor 2 isoform A [Homo sapiens]; (1234:) chemokine (C-C motif) receptor 2 isoform B [Homo sapiens]; (1235:) chemokine (C-X3-C motif) ligand 1 [Homo sapiens]; (1236:) chemokine (C-X-C motif) ligand 12 (stromal cell-derived factor 1)isoform alpha [Homo sapiens]; (1237:) chemokine (C-X-C motif) ligand 12 (stromal cell-derived factor 1)isoform beta [Homo sapiens]; (1238:) chemokine (C-X-C motif) ligand 12 (stromal cell-derived factor 1)isoform gamma [Homo sapiens]; (1239:) Chemokine receptor-like 1 (G-protein

coupled receptor DEZ)(G-protein coupled receptor ChemR23); (1240:) Chemokine receptor-like 2 (G-protein coupled receptor 30)(IL8-related receptor DRY12) (Flow-induced endothelial G-proteincoupled receptor) (FEG-1) (GPCR-BR); (1241:) Chemokine XC receptor 1 (XC chemokine receptor 1) (Lymphotactinreceptor) (G-protein coupled receptor 5); (1242:) Chemokine-binding protein 2 (Chemokine-binding protein D6) (C-Cchemokine receptor D6) (Chemokine receptor CCR-9) (Chemokinereceptor CCR-10); (1243:) chitotriosidase [Homo sapiens]; (1244:) chitotriosidase precursor [Homo sapiens]; (1245:) Chitotriosidase-1 precursor (Chitinase-1); (1246:) chloride channel 6 isoform ClC-6a [Homo sapiens]; (1247:) chloride channel 6 isoform ClC-6b [Homo sapiens]; (1248:) chloride channel 6 isoform ClC-6c [Homo sapiens]; (1249:) chloride channel 6 isoform ClC-6d [Homo sapiens]; (1250:) cholecystokinin A receptor [Homo sapiens]; (1251:) cholecystokinin preproprotein [Homo sapiens]; (1252:) Cholecystokinin type A receptor (CCK-A receptor) (CCK-AR)(Cholecystokinin-1 receptor) (CCK1-R); (1253:) cholesterol 25-hydroxylase [Homo sapiens]; (1254:) cholesterol side-chain cleavage enzyme P450scc (EC 1.14.15.67); (1255:) choline acetyltransferase [Homo sapiens]; (1256:) choline acetyltransferase isoform 1 [Homo sapiens]; (1257:) choline acetyltransferase isoform 2 [Homo sapiens]; (1258:) choline kinase alpha isoform a [Homo sapiens]; (1259:) choline kinase alpha isoform b [Homo sapiens]; (1260:) Choline O-acetyltransferase (CHOACTase) (Choline acetylase) (ChAT); (1261:) choline phosphotransferase 1 [Homo sapiens]; (1262:) choline/ethanolamine kinase isoform a [Homo sapiens]; (1263:) choline/ethanolamine kinase isoform b [Homo sapiens]; (1264:) Choline-phosphate cytidylyltransferase A (Phosphorylcholinetransferase A) (CTP:phosphocholine cytidylyltransferase A) (CT A)(CCT A) (CCT-alpha); (1265:) cholinephosphotransferase [Homo sapiens]; (1266:) cholinergic receptor, nicotinic, alpha 4 subunit precursor [Homosapiens]; (1267:) Cholinesterase precursor (Acylcholine acylhydrolase) (Cholineesterase II) (Butyrylcholine esterase) (Pseudocholinesterase); (1268:) chondroitin beta1,4 N-acetylgalactosaminyltransferase [Homosapiens]; (1269:) chondroitin beta1,4 N-acetylgalactosaminyltransferase 2 [Homosapiens]; (1270:) Chondroitin beta-1,4-N-acetylgalactosaminyltransferase 1(beta4GalNAcT-1); (1271:) Chondroitin beta-1,4-N-acetylgalactosaminyltransferase 2(GalNAcT-2) (beta4GalNAcT-2); (1272:) chondroitin sulfate proteoglycan 2 (versican) [Homo sapiens]; (1273:) chondroitin sulfate synthase 3 [Homo sapiens]; (1274:) chromatin-specific transcription elongation factor large subunit[Homo sapiens]; (1275:) chymase 1, mast cell preproprotein [Homo sapiens]; (1276:) Chymase precursor (Mast cell protease I);

(1277:) chymotrypsin-like [Homo sapiens]; (1278:) Chymotrypsin-like serine proteinase (LCLP); (1279:) Ciliary neurotrophic factor receptor alpha precursor (CNTFR alpha); (1280:) citrate synthase precursor, isoform a [Homo sapiens]; (1281:) citrate synthase precursor, isoform b [Homo sapiens]; (1282:) Class B basic helix-loop-helix protein 2 (bHLHB2) (Differentiallyexpressed in chondrocytes protein 1) (DEC1) (Enhancer-of-split andhairy-related protein 2) (SHARP-2) (Stimulated with retinoic acid13); (1283:) class I alcohol dehydrogenase, alpha subunit [Homo sapiens]; (1284:) class I alcohol dehydrogenase, gamma subunit [Homo sapiens]; (1285:) class II alcohol dehydrogenase 4 pi subunit [Homo sapiens]; (1286:) class III alcohol dehydrogenase 5 chi subunit [Homo sapiens]; (1287:) class IV alcohol dehydrogenase 7 mu or sigma subunit [Homosapiens]; (1288:) class IV alcohol dehydrogenase, sigma sigma-ADH; (1289:) clathrin heavy chain 1 [Homo sapiens]; (1290:) CLCN6 [Homo sapiens]; (1291:) CMH-1; (1292:) CMP-N-acetylneuraminate-beta-galactosamide-alpha-2,6-sialyltransferase (Beta-galactoside alpha-2,6-sialyltransferase)(Alpha 2,6-ST) (Sialyltransferase 1) (ST6Gal I) (B-cell antigenCD75); (1293:) CMRF35-H antigen precursor (CMRF35-H9) (CMRF-35-H9) (CD300aantigen) (Inhibitory receptor protein 60) (IRp60) (IRC1/IRC2) (NKinhibitory receptor); (1294:) CMRF35-like-molecule 1 precursor (CLM-1) (Immune receptor expressedon myeloid cells protein 1) (IREM-1) (Immunoglobulin superfamilymember 13) (NK inhibitory receptor) (CD300 antigen like familymember F) (IgSF13); (1295:) c-myc binding protein [Homo sapiens]; (1296:) coactivator-associated arginine methyltransferase 1 [Homo sapiens]; (1297:) coactosin-like 1 [Homo sapiens]; (1298:) coagulation factor II (thrombin) receptor-like 1 precursor [Homosapiens]; (1299:) coagulation factor II precursor [Homo sapiens]; (1300:) coagulation factor III precursor [Homo sapiens]; (1301:) coagulation factor IX [Homo sapiens]; (1302:) coagulation factor V precursor [Homo sapiens]; (1303:) coagulation factor VII isoform a precursor [Homo sapiens]; (1304:) coagulation factor VII isoform b precursor [Homo sapiens]; (1305:) coagulation factor VIII isoform a precursor [Homo sapiens]; (1306:) coagulation factor VIII isoform b precursor [Homo sapiens]; (1307:) coagulation factor X preproprotein [Homo sapiens]; (1308:) coagulation factor XIII A1 subunit precursor [Homo sapiens]; (1309:) coagulation factor XIII B subunit precursor [Homo sapiens]; (1310:) COASY protein [Homo sapiens]; (1311:) Coenzyme A synthase [Homo sapiens]; (1312:) coenzyme A synthase isoform a [Homo sapiens]; (1313:) coenzyme A synthase isoform b [Homo sapiens]; (1314:) Cofactor required for Sp1 transcriptional activation subunit 9(Transcriptional coactivator CRSP33) (RNA polymerasetranscriptional regulation mediator subunit 7

homolog) (hMED7)(Activator-recruited cofactor 34 kDa component) (ARC34); (1315:) coilin-interacting nuclear ATPase protein [Homo sapiens]; (1316:) coilin-interacting nulcear ATPase protein [Homo sapiens]; (1317:) Colipase precursor; (1318:) colony stimulating factor 3 isoform a precursor [Homo sapiens]; (1319:) colony stimulating factor 3 isoform b precursor [Homo sapiens]; (1320:) colony stimulating factor 3 isoform c [Homo sapiens]; (1321:) colony-stimulating factor; (1322:) complement C1r activated form; (1323:) "Complement C1r subcomponent precursor (Complement component 1, rsubcomponent) [Contains:) Complement C1r subcomponent heavy chain;Complement C1r subcomponent light chain]."; (1324:) complement component 1, s subcomponent [Homo sapiens]; (1325:) complement component 3 precursor [Homo sapiens]; (1326:) Complement component 6 precursor [Homo sapiens]; (1327:) Complement component C1q receptor precursor (Complement component 1q subcomponent receptor 1) (C1qR) (C1qRp) (C1qR(p)) (C1q/MBL/SPAreceptor) (CD93 antigen) (CDw93); (1328:) complement factor D preproprotein [Homo sapiens]; (1329:) Complement receptor type 1 precursor (C3b/C4b receptor) (CD35antigen); (1330:) Complement receptor type 2 precursor (Cr2) (Complement C3dreceptor) (Epstein-Barr virus receptor) (EBV receptor) (CD21antigen); (1331:) copper monamine oxidase; (1332:) coproporphyrinogen oxidase [Homo sapiens]; (1333:) core 2 beta-1,6-N-acetylglucosaminyltransferase 3 [Homo sapiens]; (1334:) corin [Homo sapiens]; (1335:) Corticosteroid 11-beta-dehydrogenase isozyme 1 (11-DH)(11-beta-hydroxysteroid dehydrogenase 1) (11-beta-HSD1); (1336:) Corticosteroid 11-beta-dehydrogenase isozyme 2 (11-DH2)(11-beta-hydroxysteroid dehydrogenase type 2) (11-beta-HSD2)(NAD-dependent 11-beta-hydroxysteroid dehydrogenase); (1337:) Corticotropin-releasing factor receptor 1 precursor (CRF-R) (CRF1)(Corticotropin-releasing hormone receptor 1) (CRH-R 1); (1338:) Corticotropin-releasing factor receptor 2 precursor (CRF-R 2)(CRF2) (Corticotropin-releasing hormone receptor 2) (CRH-R 2); (1339:) COUP transcription factor 1 (COUP-TF1) (COUP-TF I) (V-ERBA-relatedprotein EAR-3); (1340:) COUP transcription factor 2 (COUP-TF2) (COUP-TF II) (ApolipoproteinAI regulatory protein 1) (ARP-1); (1341:) COX11 homolog [Homo sapiens]; (1342:) Coxsackievirus and adenovirus receptor precursor (CoxsackievirusB-adenovirus receptor) (hCAR) (CVB3-binding protein) (HCVADR); (1343:) CPA4 protein [Homo sapiens]; (1344:) C-reactive protein, pentraxin-related [Homo sapiens]; (1345:) CREB binding protein [Homo sapiens]; (1346:) CRSP complex subunit 2 (Cofactor required for Sp1 transcriptionalactivation subunit 2) (Transcriptional coactivator CRSP150)(Vitamin D3 receptor-interacting protein complex 150 kDa component)(DRIP150) (Thyroid

hormone receptor-associated protein complex 170kDa component) (Trap170) (Activator-recruited cofactor 150 kDacomponent) (ARC150); (1347:) CRSP complex subunit 3 (Cofactor required for Sp1 transcriptionalactivation subunit 3) (Transcriptional coactivator CRSP130)(Vitamin D3 receptor-interacting protein complex 130 kDa component)(DRIP130) (Activator-recruited cofactor 130 kDa component)(ARC130); (1348:) CRSP complex subunit 6 (Cofactor required for Sp1 transcriptionalactivation subunit 6) (Transcriptional coactivator CRSP77) (VitaminD3 receptor-interacting protein complex 80 kDa component) (DRIP80)(Thyroid hormone receptor-associated protein complex 80 kDacomponent) (Trap80) (Activator-recruited cofactor 77 kDa component)(ARC77); (1349:) CRSP complex subunit 7 (Cofactor required for Sp1 transcriptionalactivation subunit 7) (Transcriptional coactivator CRSP70)(Activator-recruited cofactor 70 kDa component) (ARC70); (1350:) crystallin, alpha A [Homo sapiens]; (1351:) crystallin, alpha B [Homo sapiens]; (1352:) crystallin, beta A2 [Homo sapiens]; (1353:) crystallin, beta A3 [Homo sapiens]; (1354:) crystallin, beta A4 [Homo sapiens]; (1355:) crystallin, beta B1 [Homo sapiens]; (1356:) crystallin, beta B2 [Homo sapiens]; (1357:) crystallin, beta B3 [Homo sapiens]; (1358:) crystallin, gamma A [Homo sapiens]; (1359:) crystallin, gamma B [Homo sapiens]; (1360:) crystallin, gamma C [Homo sapiens]; (1361:) crystallin, gamma D [Homo sapiens]; (1362:) crystallin, gamma S [Homo sapiens]; (1363:) crystallin, mu isoform 1 [Homo sapiens]; (1364:) crystallin, mu isoform 2 [Homo sapiens]; (1365:) crystallin, zeta [Homo sapiens]; (1366:) c-src tyrosine kinase [Homo sapiens]; (1367:) CTP synthase [Homo sapiens]; (1368:) CTP synthase 1 (UTP--ammonia ligase 1) (CTP synthetase 1); (1369:) CTP synthase 2 (UTP--ammonia ligase 2) (CTP synthetase 2); (1370:) C-type lectin domain family 4 member F (C-type lectin superfamilymember 13) (C-type lectin 13); (1371:) C-type lectin domain family 4 member M (CD209 antigen-like protein1) (Dendritic cell-specific ICAM-3-grabbing nonintegrin 2)(DC-SIGN2) (DC-SIGN-related protein) (DC-SIGNR) (Liver/lymphnode-specific ICAM-3-grabbing nonintegrin) (L-SIGN) (CD299antigen); (1372:) C-type lectin domain family 9 member A; (1373:) Cubilin precursor (Intrinsic factor-cobalamin receptor) (Intrinsicfactor-vitamin B12 receptor) (460 kDa receptor) (Intestinalintrinsic factor receptor); (1374:) Cullin-1 (CUL-1); (1375:) Cullin-2 (CUL-2); (1376:) Cullin-5 (CUL-5) (Vasopressin-activated calcium-mobilizingreceptor) (VACM-1); (1377:) CX3C chemokine receptor 1 (C-X3-C CKR-1) (CX3CR1) (Fractalkinereceptor) (G-protein coupled receptor 13) (V28) (Beta chemokinereceptor-like 1) (CMK-BRL-1) (CMKBLR1); (1378:) C-X-C chemokine receptor type 3 (CXC-R3) (CXCR-

3)(Interferon-inducible protein 10 receptor) (IP-10 receptor)(CKR-L2) (CD183 antigen) (G protein-coupled receptor 9); (1379:) C-X-C chemokine receptor type 4 (CXC-R4) (CXCR-4) (Stromalcell-derived factor 1 receptor) (SDF-1 receptor) (Fusin)(Leukocyte-derived seven transmembrane domain receptor) (LESTR)(LCR1) (FB22) (NPYRL) (HM89) (CD184 antigen); (1380:) C-X-C chemokine receptor type 5 (CXC-R5) (CXCR-5) (Burkitt lymphomareceptor 1) (Monocyte-derived receptor 15) (MDR-15) (CD185antigen); (1381:) C-X-C chemokine receptor type 6 (CXC-R6) (CXCR-6) (G-proteincoupled receptor bonzo) (G-protein coupled receptor STRL33) (CD186antigen) (CDw186); (1382:) C-X-C chemokine receptor type 7 (CXC-R7) (CXCR-7) (G-proteincoupled receptor RDC1 homolog) (RDC-1) (Chemokine orphan receptor1) (G-protein coupled receptor 159); (1383:) cyclin D1 [Homo sapiens]; (1384:) cyclin-dependent kinase 2 isoform 1 [Homo sapiens]; (1385:) cyclin-dependent kinase 2 isoform 2 [Homo sapiens]; (1386:) cyclin-dependent kinase inhibitor 1B [Homo sapiens]; (1387:) cyclin-dependent kinase inhibitor 2A isoform 1 [Homo sapiens]; (1388:) cyclin-dependent kinase inhibitor 2A isoform 3 [Homo sapiens]; (1389:) cyclin-dependent kinase inhibitor 2A isoform 4 [Homo sapiens]; (1390:) Cyclin-dependent kinase inhibitor 2A, isoform 4 (p14ARF) (p19ARF); (1391:) Cyclin-dependent kinase-like 5 (Serine/threonine-protein kinase 9); (1392:) cyclin-selective ubiquitin carrier protein [Homo sapiens]; (1393:) Cystathionase (cystathionine gamma-lyase) [Homo sapiens]; (1394:) cystathionase isoform 1 [Homo sapiens]; (1395:) cystathionase isoform 1 variant [Homo sapiens]; (1396:) cystathionase isoform 2 [Homo sapiens]; (1397:) cystathionine B synthase [Homo sapiens]; (1398:) Cystathionine beta-synthase (Serine sulfhydrase) (Beta-thionase); (1399:) cystathionine beta-synthase major isoform [Homo sapiens]; (1400:) cystathionine beta-synthase; (1401:) Cystathionine gamma-lyase (Gamma-cystathionase); (1402:) "cystathionine gamma-lyase; cystathionase [Homo sapiens]."; (1403:) cystathionine-beta-synthase [Homo sapiens]; (1404:) Cystatin C precursor (Neuroendocrine basic polypeptide)(Gamma-trace) (Post-gamma-globulin); (1405:) "cysteine conjugate-beta lyase; cytoplasmic (glutamine transaminaseK, kyneurenine aminotransferase) [Homo sapiens]."; (1406:) cysteine desulfurase [Homo sapiens]; (1407:) Cysteine desulfurase, mitochondrial precursor; (1408:) cysteine dioxygenase [Homo sapiens]; (1409:) Cysteine protease ATG4A (Autophagy-related protein 4 homolog A)(hAPG4A) (Autophagin-2) (Autophagy-related cysteine endopeptidase2) (AUT-like 2 cysteine endopeptidase); (1410:) Cysteine protease ATG4B (Autophagy-related protein 4 homolog B)(hAPG4B) (Autophagin-1) (Autophagy-related cysteine endopeptidase1) (AUT-like 1 cysteine

endopeptidase); (1411:) Cysteine protease ATG4C (Autophagy-related protein 4 homolog C)(Autophagin-3) (Autophagy-related cysteine endopeptidase 3)(AUT-like 3 cysteine endopeptidase); (1412:) Cysteine protease ATG4D (Autophagy-related protein 4 homolog D)(Autophagin-4) (Autophagy-related cysteine endopeptidase 4)(AUT-like 4 cysteine endopeptidase); (1413:) cysteine protease CPP32 isoform alpha; (1414:) cysteine protease CPP32 isoform beta; (1415:) cysteine protease Mch2 isoform alpha; (1416:) cysteine protease Mch2 isoform beta; (1417:) cysteine protease; (1418:) cysteine-rich, angiogenic inducer, 61 [Homo sapiens]; (1419:) Cysteinyl leukotriene receptor 1 (CysLTR1) (Cysteinyl leukotrieneD4 receptor) (LTD4 receptor) (HG55) (HMTMF81); (1420:) Cysteinyl leukotriene receptor 2 (CysLTR2) (HG57) (HPN321)(hGPCR21); (1421:) cytidine 5'-monophosphate N-acetylneuraminic acid synthetase [Homosapiens]; (1422:) Cytidine deaminase (Cytidine aminohydrolase); (1423:) cytidine deaminase [Homo sapiens]; (1424:) Cytidine monophosphate-N-acetylneuraminic acid hydroxylase-likeprotein (CMP-NeuAc hydroxylase-like protein); (1425:) cytidine triphosphate synthase II [Homo sapiens]; (1426:) cytidylate kinase [Homo sapiens]; (1427:) cytochrome b [Homo sapiens]; (1428:) cytochrome b, alpha polypeptide [Homo sapiens]; (1429:) Cytochrome b; (1430:) cytochrome b5 reductase b5R.2 [Homo sapiens]; (1431:) cytochrome b5 reductase isoform 1 [Homo sapiens]; (1432:) cytochrome b5 reductase isoform 2 [Homo sapiens]; (1433:) cytochrome c [Homo sapiens]; (1434:) Cytochrome c oxidase subunit 1 (Cytochrome c oxidase polypeptideI); (1435:) Cytochrome c oxidase subunit 2 (Cytochrome c oxidase polypeptideII); (1436:) Cytochrome c oxidase subunit 3 (Cytochrome c oxidase polypeptideIII); (1437:) cytochrome c oxidase subunit 8A [Homo sapiens]; (1438:) cytochrome c oxidase subunit IV isoform 1 precursor [Homo sapiens]; (1439:) cytochrome c oxidase subunit IV isoform 2 [Homo sapiens]; (1440:) cytochrome c oxidase subunit IV precursor [Homo sapiens]; (1441:) cytochrome c oxidase subunit Va precursor [Homo sapiens]; (1442:) cytochrome c oxidase subunit Vb precursor [Homo sapiens]; (1443:) cytochrome c oxidase subunit VIa polypeptide 1 precursor [Homosapiens]; (1444:) cytochrome c oxidase subunit VIa polypeptide 2 precursor [Homosapiens]; (1445:) cytochrome c oxidase subunit VIb [Homo sapiens]; (1446:) cytochrome c oxidase subunit VIc proprotein [Homo sapiens]; (1447:) cytochrome c-1 [Homo sapiens]; (1448:) cytochrome P450 [Homo sapiens]; (1449:) Cytochrome P450 11A1, mitochondrial precursor (CYPXIA1) (P450(scc))(Cholesterol side-chain cleavage enzyme) (Cholesterol desmolase); (1450:) Cytochrome P450 11B2, mitochondrial precursor (CYPXIB2) (P-450Aldo)(Aldosterone synthase) (ALDOS)

(Aldosterone-synthesizing enzyme)(Steroid 18-hydroxylase) (P-450C18); (1451:) Cytochrome P450 17A1 (CYPXVII) (P450-C17) (P450c17) (Steroid17-alpha-monooxygenase) (Steroid 17-alpha-hydroxylase/17,20 lyase); (1452:) Cytochrome P450 19A1 (Aromatase) (CYPXIX) (Estrogen synthetase)(P-450AROM); (1453:) Cytochrome P450 1A1 (CYPIA1) (P450-P1) (P450 form 6) (P450-C); (1454:) cytochrome P450 1A1 variant [Homo sapiens]; (1455:) Cytochrome P450 1A2 (CYPIA2) (P450-P3) (P(3)450) (P450 4); (1456:) Cytochrome P450 1B1 (CYPIB1); (1457:) Cytochrome P450 21 (Cytochrome P450 XXI) (Steroid 21-hydroxylase)(21-OHase) (P450-C21) (P-450c21) (P450-C21B); (1458:) Cytochrome P450 26A1 (Retinoic acid-metabolizing cytochrome) (P450retinoic acid-inactivating 1) (P450RAI) (hP450RAI) (Retinoic acid4-hydroxylase); (1459:) Cytochrome P450 26B1 (P450 26A2) (P450 retinoic acid-inactivating2) (P450RAI-2) (Retinoic acid-metabolizing cytochrome); (1460:) Cytochrome P450 27, mitochondrial precursor (CytochromeP-450C27/25) (Sterol 26-hydroxylase) (Sterol 27-hydroxylase)(Vitamin D(3) 25-hydroxylase)(5-beta-cholestane-3-alpha,7-alpha,12-alpha-triol 27-hydroxylase); (1461:) cytochrome P450 2A3, hepatic - human (fragment); (1462:) Cytochrome P450 2A7 (CYPIIA7) (P450-IIA4); (1463:) Cytochrome P450 2B6 (CYPIIB6) (P450 IIB1); (1464:) Cytochrome P450 2C18 (CYPIIC18) (P450-6B/29C); (1465:) Cytochrome P450 2C8 (CYPIIC8) (P450 form 1) (P450 MP-12/MP-20)(P450 IIC2) (S-mephenytoin 4-hydroxylase); (1466:) Cytochrome P450 2C9 ((R)-limonene 6-monooxygenase) ((S)-limonene6-monooxygenase) ((S)-limonene 7-monooxygenase) (CYPIIC9) (P450PB-1) (P450 MP-4/MP-8) (S-mephenytoin 4-hydroxylase) (P-450MP); (1467:) Cytochrome P450 2E1 (CYPIIE1) (P450-J); (1468:) Cytochrome P450 2J2 (CYPIIJ2) (Arachidonic acid epoxygenase); (1469:) Cytochrome P450 2R1 (Vitamin D 25-hydroxylase); (1470:) Cytochrome P450 3A3 (CYPIIIA3) (HLp); (1471:) Cytochrome P450 3A4 (Quinine 3-monooxygenase) (CYPIIIA4)(Nifedipine oxidase) (Taurochenodeoxycholate 6-alpha-hydroxylase)(NF-25) (P450-PCN1); (1472:) Cytochrome P450 3A5 (CYPIIIA5) (P450-PCN3) (HLp2); (1473:) Cytochrome P450 3A7 (CYPIIIA7) (P450-HFLA); (1474:) Cytochrome P450 4A11 precursor (CYPIVA11) (Fatty acidomega-hydroxylase) (P-450 HK omega) (Lauric acid omega-hydroxylase)(CYP4AII) (P450-HL-omega); (1475:) Cytochrome P450 4B1 (CYPIVB1) (P450-HP); (1476:) Cytochrome P450 4F2 (CYPIVF2) (Leukotriene-B(4) omega-hydroxylase)(Leukotriene-B(4) 20-monooxygenase) (Cytochrome P450-LTB-omega); (1477:) Cytochrome P450 4F3 (CYPIVF3) (Leukotriene-B(4) omega-hydroxylase)(Leukotriene-B(4) 20-monooxygenase) (Cytochrome P450-LTB-omega); (1478:) cytochrome P450 family 1 subfamily A

polypeptide 1 [Homo sapiens]; (1479:) cytochrome P450 family 3 subfamily A polypeptide 4 [Homo sapiens]; (1480:) cytochrome P450 reductase [Homo sapiens]; (1481:) cytochrome P450, family 1, subfamily A, polypeptide 1 [Homosapiens]; (1482:) cytochrome P450, family 1, subfamily A, polypeptide 2 [Homosapiens]; (1483:) cytochrome P450, family 1, subfamily B, polypeptide 1 [Homosapiens]; (1484:) cytochrome P450, family 11, subfamily B, polypeptide 1 isoform 1precursor [Homo sapiens]; (1485:) cytochrome P450, family 11, subfamily B, polypeptide 1 isoform 2precursor [Homo sapiens]; (1486:) cytochrome P450, family 17 [Homo sapiens]; (1487:) cytochrome P450, family 19 [Homo sapiens]; (1488:) cytochrome P450, family 2, subfamily A, polypeptide 6 [Homosapiens]; (1489:) cytochrome P450, family 2, subfamily B, polypeptide 6 [Homosapiens]; (1490:) cytochrome P450, family 2, subfamily C, polypeptide 18 [Homosapiens]; (1491:) cytochrome P450, family 2, subfamily C, polypeptide 19 [Homosapiens]; (1492:) cytochrome P450, family 2, subfamily C, polypeptide 8 [Homosapiens]; (1493:) cytochrome P450, family 2, subfamily C, polypeptide 9 [Homosapiens]; (1494:) cytochrome P450, family 2, subfamily D, polypeptide 6 isoform 1[Homo sapiens]; (1495:) cytochrome P450, family 2, subfamily D, polypeptide 6 isoform 2[Homo sapiens]; (1496:) cytochrome P450, family 2, subfamily E, polypeptide 1 [Homosapiens]; (1497:) cytochrome P450, family 2, subfamily J, polypeptide 2 [Homosapiens]; (1498:) cytochrome P450, family 2, subfamily R, polypeptide 1 [Homosapiens]; (1499:) cytochrome P450, family 2, subfamily U, polypeptide 1 [Homosapiens]; (1500:) cytochrome P450, family 2, subfamily W, polypeptide 1 [Homosapiens]; (1501:) cytochrome P450, family 21, subfamily A, polypeptide 2 [Homosapiens]; (1502:) cytochrome P450, family 24 precursor [Homo sapiens]; (1503:) cytochrome P450, family 26, subfamily A, polypeptide 1 isoform 1[Homo sapiens]; (1504:) cytochrome P450, family 26, subfamily A, polypeptide 1 isoform 2[Homo sapiens]; (1505:) cytochrome P450, family 26, subfamily b, polypeptide 1 [Homosapiens]; (1506:) cytochrome P450, family 26, subfamily C, polypeptide 1 [Homosapiens]; (1507:) cytochrome P450, family 27, subfamily A, polypeptide 1 precursor[Homo sapiens]; (1508:) cytochrome P450, family 27, subfamily B, polypeptide 1 [Homosapiens]; (1509:) cytochrome P450, family 3, subfamily A, polypeptide 43 isoform 1[Homo sapiens]; (1510:) cytochrome P450, family 3, subfamily A, polypeptide 43 isoform 2[Homo sapiens]; (1511:) cytochrome P450, family 3, subfamily A, polypeptide 43 isoform 3[Homo sapiens]; (1512:) cytochrome P450, family 3, subfamily A, polypeptide 5 [Homosapiens]; (1513:) cytochrome P450, family 3, subfamily A, polypeptide 7 [Homosapiens]; (1514:) cytochrome P450,

family 4, subfamily A, polypeptide 11 [Homosapiens]; (1515:) cytochrome P450, family 4, subfamily F, polypeptide 12 [Homosapiens]; (1516:) cytochrome P450, family 4, subfamily F, polypeptide 2 [Homosapiens]; (1517:) cytochrome P450, family 4, subfamily F, polypeptide 3 [Homosapiens]; (1518:) cytochrome P450, family 46 [Homo sapiens]; (1519:) cytochrome P450, family 7, subfamily A, polypeptide 1 [Homosapiens]; (1520:) cytochrome P450, family 7, subfamily B, polypeptide 1 [Homosapiens]; (1521:) cytochrome P450, subfamily IIIA, polypeptide 4 [Homo sapiens]; (1522:) cytochrome P450, subfamily XIA precursor [Homo sapiens]; (1523:) cytochrome P450, subfamily XIB polypeptide 2 precursor [Homosapiens]; (1524:) cytochrome P450; (1525:) cytochrome P450j; (1526:) Cytokine receptor common beta chain precursor (GM-CSF/IL-3/IL-5receptor common beta-chain) (CD131 antigen) (CDw131); (1527:) Cytokine receptor common gamma chain precursor (Gamma-C)(Interleukin-2 receptor gamma chain) (IL-2R gamma chain) (p64)(CD132 antigen); (1528:) Cytokine receptor-like factor 1 precursor (Cytokine-like factor 1)(CLF-1) (ZcytoR5); (1529:) Cytokine receptor-like factor 2 precursor (Cytokine receptor-like2) (CRL2) (IL-XR) (Thymic stromal lymphopoietin protein receptor)(TSLPR); (1530:) cytoplasmic cysteine conjugate-beta lyase [Homo sapiens]; (1531:) Cytoplasmic dynein 1 light intermediate chain 1 (Dynein lightintermediate chain 1, cytosolic) (Dynein light chain A) (DLC-A); (1532:) Cytosol aminopeptidase (Leucine aminopeptidase) (LAP) (Leucylaminopeptidase) (Proline aminopeptidase) (Prolyl aminopeptidase)(Peptidase S); (1533:) Cytosolic 5'-nucleotidase 1A (Cytosolic 5'-nucleotidase IA) (cN1A)(cN-IA) (cN-I); (1534:) Cytosolic 5'-nucleotidase 1B (Cytosolic 5'-nucleotidase IB) (cN1B)(cN-IB) (Autoimmune infertility-related protein); (1535:) cytosolic acetyl-CoA hydrolase [Homo sapiens]; (1536:) cytosolic aminopeptidase P [Homo sapiens]; (1537:) Cytosolic beta-glucosidase (Cytosolic beta-glucosidase-like protein1); (1538:) cytosolic beta-glucosidase [Homo sapiens]; (1539:) cytosolic inhibitor of NRF2 [Homo sapiens]; (1540:) cytosolic leucyl-tRNA synthetase [Homo sapiens]; (1541:) cytosolic malic enzyme 1 [Homo sapiens]; (1542:) cytosolic malic enzyme 1 variant [Homo sapiens]; (1543:) cytosolic malic enzyme; (1544:) cytosolic NADP(+)-dependent malic enzyme; (1545:) cytosolic ovarian carcinoma antigen 1 isoform a [Homo sapiens]; (1546:) cytosolic ovarian carcinoma antigen 1 isoform b [Homo sapiens]; (1547:) cytosolic phosphoenolpyruvate carboxykinase 1 [Homo sapiens]; (1548:) "Cytosolic phospholipase A2 (cPLA2) (Phospholipase A2 group IVA)[Includes:) Phospholipase A2 (Phosphatidylcholine 2-acylhydrolase);Lysophospholipase]."; (1549:) Cytosolic phospholipase A2 beta

(cPLA2-beta) (Phospholipase A2group IVB); (1550:) Cytosolic phospholipase A2 delta (cPLA2-delta) (Phospholipase A2group IVD); (1551:) Cytosolic phospholipase A2 epsilon (cPLA2-epsilon) (PhospholipaseA2 group IVE); (1552:) Cytosolic phospholipase A2 gamma precursor (cPLA2-gamma)(Phospholipase A2 group IVC); (1553:) Cytosolic phospholipase A2 zeta (cPLA2-zeta) (Phospholipase A2group IVF); (1554:) cytosolic phospholipase A2, group IVA [Homo sapiens]; (1555:) Cytosolic purine 5'-nucleotidase (5'-nucleotidase cytosolic II); (1556:) cytosolic thyroid hormone-binding protein (EC 2.7.1.40); (1557:) CAAX prenyl protease 1 homolog (Prenyl protein-specificendoprotease 1) (Farnesylated proteins-converting enzyme 1)(FACE-1) (Zinc metalloproteinase Ste24 homolog); (1558:) CAAX prenyl protease 2 (Prenyl protein-specific endoprotease 2)(Farnesylated proteins-converting enzyme 2) (FACE-2) (hRCE1); (1559:) D(1A) dopamine receptor; (1560:) D(1B) dopamine receptor (D(5) dopamine receptor) (D1beta dopaminereceptor); (1561:) D(2) dopamine receptor (Dopamine D2 receptor); (1562:) D(3) dopamine receptor; (1563:) D(4) dopamine receptor (Dopamine D4 receptor) (D(2C) dopaminereceptor); (1564:) D-2-hydroxyglutarate dehydrogenase, mitochondrial precursor; (1565:) dachshund homolog 1 isoform a [Homo sapiens]; (1566:) dachshund homolog 1 isoform b [Homo sapiens]; (1567:) dachshund homolog 1 isoform c [Homo sapiens]; (1568:) D-amino-acid oxidase [Homo sapiens]; (1569:) D-aspartate oxidase isoform a [Homo sapiens]; (1570:) D-aspartate oxidase isoform b [Homo sapiens]; (1571:) D-beta-hydroxybutyrate dehydrogenase, mitochondrial precursor (BDH)(3-hydroxybutyrate dehydrogenase); (1572:) DCP1 decapping enzyme homolog A [Homo sapiens]; (1573:) DCP1 decapping enzyme homolog B (S. cerevisiae) [Homo sapiens]; (1574:) DCP2 decapping enzyme [Homo sapiens]; (1575:) D-dopachrome decarboxylase (D-dopachrome tautomerase)(Phenylpyruvate tautomerase II); (1576:) D-dopachrome tautomerase [Homo sapiens]; (1577:) DEAD/H (Asp-Glu-Ala-Asp/His) box polypeptide 11 isoform 1 [Homosapiens]; (1578:) DEAD/H (Asp-Glu-Ala-Asp/His) box polypeptide 11 isoform 2 [Homosapiens]; (1579:) deaminase,adenosine; (1580:) Death-associated protein kinase 1 (DAP kinase 1); (1581:) Death-associated protein kinase 2 (DAP kinase 2)(DAP-kinase-related protein 1) (DRP-1); (1582:) Debranching enzyme homolog 1 (S. cerevisiae) [Homo sapiens]; (1583:) debranching enzyme homolog 1 [Homo sapiens]; (1584:) decapping enzyme Dcp1b [Homo sapiens]; (1585:) decapping enzyme hDcp1a [Homo sapiens]; (1586:) decapping enzyme hDcp1b [Homo sapiens]; (1587:) decapping enzyme hDcp2 [Homo sapiens]; (1588:) Decapping enzyme, scavenger [Homo sapiens]; (1589:)

defender against cell death 1 [Homo sapiens]; (1590:) defensin, alpha 5 preproprotein [Homo sapiens]; (1591:) Dehydrogenase/reductase SDR family member 8 precursor(17-beta-hydroxysteroid dehydrogenase 11) (17-beta-HSD 11)(17-beta-HSD XI) (17betaHSDXI) (17bHSD11) (17betaHSD11) (Retinalshort-chain dehydrogenase/reductase 2) (retSDR2) (Cutaneous T-celllymphoma-associated antigen HD-CL-03) (CTCL tumor antigenHD-CL-03); (1592:) deiodinase, iodothyronine, type I isoform a [Homo sapiens]; (1593:) deiodinase, iodothyronine, type I isoform b [Homo sapiens]; (1594:) deiodinase, iodothyronine, type I isoform c [Homo sapiens]; (1595:) deiodinase, iodothyronine, type I isoform d [Homo sapiens]; (1596:) deiodinase, iodothyronine, type II isoform a [Homo sapiens]; (1597:) deiodinase, iodothyronine, type II isoform b [Homo sapiens]; (1598:) deiodinase, iodothyronine, type III [Homo sapiens]; (1599:) "Delta 1-pyrroline-5-carboxylate synthetase (P5CS) (Aldehydedehydrogenase 18 family member A1) [Includes:) Glutamate 5-kinase(Gamma-glutamyl kinase) (GK); Gamma-glutamyl phosphate reductase(GPR) (Glutamate-5-semialdehyde dehydrogenase)(Glutamyl-gamma-semialdehyde dehydrogenase)]."; (1600:) delta 4-3-oxosteroid 5 beta-reductase [Homo sapiens]; (1601:) delta- aminolevulinate synthase (housekeeping) [Homo sapiens]; (1602:) Delta and Notch-like epidermal growth factor-related receptorprecursor; (1603:) delta isoform of regulatory subunit B56, protein phosphatase 2Aisoform 1 [Homo sapiens]; (1604:) delta isoform of regulatory subunit B56, protein phosphatase 2Aisoform 2 [Homo sapiens]; (1605:) delta isoform of regulatory subunit B56, protein phosphatase 2Aisoform 3 [Homo sapiens]; (1606:) Delta-1-pyrroline-5-carboxylate dehydrogenase, mitochondrialprecursor (P5C dehydrogenase) (Aldehyde dehydrogenase 4A1); (1607:) delta3, delta2-enoyl-CoA isomerase; (1608:) Delta4-3-oxosteroid 5beta reductase; (1609:) Delta-aminolevulinic acid dehydratase (Porphobilinogen synthase)(ALADH); (1610:) delta-aminolevulinic acid dehydratase isoform a [Homo sapiens]; (1611:) delta-aminolevulinic acid dehydratase isoform b [Homo sapiens]; (1612:) Delta-type opioid receptor (DOR-1); (1613:) deoxy-5'-nucleotidase [Homo sapiens]; (1614:) deoxycytidine kinase [Homo sapiens]; (1615:) Deoxycytidylate deaminase (dCMP deaminase); (1616:) deoxycytidylate deaminase; (1617:) deoxyguanosine kinase isoform a precursor [Homo sapiens]; (1618:) deoxyguanosine kinase isoform b precursor [Homo sapiens]; (1619:) Deoxyhypusine hydroxylase (Deoxyhypusine monooxygenase) (hDOHH)(HEAT-like repeat-containing protein 1); (1620:) Deoxyhypusine synthase (DHS); (1621:) deoxyhypusine synthase isoform a [Homo sapiens]; (1622:) deoxyhypusine

synthase isoform b [Homo sapiens]; (1623:) deoxyhypusine synthase isoform c [Homo sapiens]; (1624:) deoxyhypusine synthase; (1625:) Deoxyribonuclease gamma precursor (DNase gamma) (DeoxyribonucleaseI-like 3) (DNase I homolog protein DHP2) (Liver and spleen DNase)(LS-DNase) (LSD); (1626:) deoxyribonuclease I precursor [Homo sapiens]; (1627:) deoxyribonuclease II, lysosomal precursor [Homo sapiens]; (1628:) deoxyribonuclease III (DNase III) [Homo sapiens]; (1629:) Deoxyribonuclease-2-alpha precursor (Deoxyribonuclease II alpha)(DNase II alpha) (Acid DNase) (Lysosomal DNase II) (R31240_2); (1630:) Deoxyuridine 5'-triphosphate nucleotidohydrolase, mitochondrialprecursor (dUTPase) (dUTP pyrophosphatase); (1631:) de-ubiquitinase [Homo sapiens]; (1632:) deubiquitinating enzyme [Homo sapiens]; (1633:) deubiquitinating enzyme 1 [Homo sapiens]; (1634:) deubiquitinating enzyme 3 [Homo sapiens]; (1635:) deubiquitinating enzyme DUB1 [Homo sapiens]; (1636:) deubiquitinating enzyme DUB2 [Homo sapiens]; (1637:) deubiquitinating enzyme DUB4 [Homo sapiens]; (1638:) Deubiquitinating Enzyme Uch-L3 (Human) At 1.8 Angstrom Resolution; (1639:) Deubiquitinating protein VCIP135 (Valosin-containing proteinp97/p47 complex-interacting protein p135) (Valosin-containingprotein p97/p47 complex-interacting protein 1); (1640:) D-glucuronyl C5-epimerase [Homo sapiens]; (1641:) Diacylglycerol kinase alpha (Diglyceride kinase alpha) (DGK-alpha)(DAG kinase alpha) (80 kDa diacylglycerol kinase); (1642:) Diacylglycerol kinase beta (Diglyceride kinase beta) (DGK-beta)(DAG kinase beta) (90 kDa diacylglycerol kinase); (1643:) Diacylglycerol kinase delta (Diglyceride kinase delta) (DGK-delta)(DAG kinase delta) (130 kDa diacylglycerol kinase); (1644:) Diacylglycerol kinase gamma (Diglyceride kinase gamma) (DGK-gamma)(DAG kinase gamma); (1645:) diacylglycerol kinase gamma [Homo sapiens]; (1646:) Diacylglycerol kinase kappa (Diglyceride kinase kappa) (DGK-kappa)(DAG kinase kappa) (142 kDa diacylglycerol kinase); (1647:) diacylglycerol kinase, beta isoform 1 [Homo sapiens]; (1648:) diacylglycerol kinase, beta isoform 2 [Homo sapiens]; (1649:) diacylglycerol kinase, delta 130kDa isoform 1 [Homo sapiens]; (1650:) diacylglycerol kinase, delta 130kDa isoform 2 [Homo sapiens]; (1651:) diacylglycerol kinase, eta isoform 1 [Homo sapiens]; (1652:) diacylglycerol kinase, eta isoform 2 [Homo sapiens]; (1653:) diacylglycerol kinase, gamma 90kDa [Homo sapiens]; (1654:) diacylglycerol kinase, iota [Homo sapiens]; (1655:) diacylglycerol O-acyltransferase 1 [Homo sapiens]; (1656:) Diacylglycerol O-acyltransferase 2 (Diglyceride acyltransferase 2); (1657:) diacylglycerol O-acyltransferase 2-like 4 [Homo sapiens]; (1658:) Diamine acetyltransferase 1 (Spermidine/spermineN(1)-acetyltransferase 1) (SSAT) (SSAT-

1) (Putrescineacetyltransferase) (Polyamine N-acetyltransferase 1); (1659:) Diamine acetyltransferase 2 (Spermidine/spermineN(1)-acetyltransferase 2) (Polyamine N-acetyltransferase 2); (1660:) diamine oxidase, copper/topa quinone containing; (1661:) diamine oxidase; (1662:) dicarbonyl/L-xylulose reductase [Homo sapiens]; (1663:) dicer1 [Homo sapiens]; (1664:) dihydrofolate reductase [Homo sapiens]; (1665:) Dihydrofolate reductase; (1666:) dihydrolipoamide acetyltransferase; (1667:) "dihydrolipoamide branched chain transacylase (E2 component ofbranched chain keto acid dehydrogenase complex; maple syrup urinedisease) [Homo sapiens]."; (1668:) Dihydrolipoamide branched chain transacylase E2 [Homo sapiens]; (1669:) dihydrolipoamide branched chain transacylase precursor [Homosapiens]; (1670:) dihydrolipoamide dehydrogenase precursor [Homo sapiens]; (1671:) dihydrolipoamide dehydrogenase-binding protein [Homo sapiens]; (1672:) dihydrolipoamide S-acetyltransferase (E2 component of pyruvatedehydrogenase complex) [Homo sapiens]; (1673:) dihydrolipoamide S-acetyltransferase (E2 component of pyruvatedehydrogenase complex) variant [Homo sapiens]; (1674:) dihydrolipoamide S-succinyltransferase (E2 component of2-oxo-glutarate complex) [Homo sapiens]; (1675:) dihydrolipoamide S-succinyltransferase (EC 2.3.1.61) - human; (1676:) dihydrolipoamide succinyltransferase [Homo sapiens]; (1677:) dihydrolipoamide succinyltransferase; (1678:) Dihydrolipoyl dehydrogenase, mitochondrial precursor(Dihydrolipoamide dehydrogenase) (Glycine cleavage system Lprotein); (1679:) dihydrolipoyl transacylase; (1680:) Dihydrolipoyllysine-residue acetyltransferase component of pyruvatedehydrogenase complex, mitochondrial precursor (Pyruvatedehydrogenase complex E2 subunit) (PDCE2) (E2) (DihydrolipoamideS-acetyltransferase component of pyruvate dehydrogenase complex)(PDC-E2) (70 kDa mitochondrial autoantigen of primary biliarycirrhosis) (PBC) (M2 antigen complex 70 kDa subunit); (1681:) Dihydrolipoyllysine-residue succinyltransferase component of2-oxoglutarate dehydrogenase complex, mitochondrial precursor(Dihydrolipoamide succinyltransferase component of 2-oxoglutaratedehydrogenase complex) (E2) (E2K); (1682:) dihydroorotate dehydrogenase isoform 1 precursor [Homo sapiens]; (1683:) dihydroorotate dehydrogenase isoform 2 precursor [Homo sapiens]; (1684:) Dihydroorotate dehydrogenase, mitochondrial precursor(Dihydroorotate oxidase) (DHOdehase); (1685:) Dihydropteridine reductase (HDHPR) (Quinoid dihydropteridinereductase); (1686:) dihydropyrimidine dehydrogenase [Homo sapiens]; (1687:) Dihydropyrimidine dehydrogenase [NADP+] precursor (DPD) (DHPDHase)(Dihydrouracil dehydrogenase) (Dihydrothymine dehydrogenase);

(1688:) dihydropyrimidine dehydrogenase; (1689:) dimerization cofactor of hepatocyte nuclear factor 1 (HNF1) frommuscle [Homo sapiens]; (1690:) dimethylaniline monooxygenase (N-oxide-forming) (EC 1.14.13.8),hepatic 2 - human; (1691:) Dimethylaniline monooxygenase [N-oxide-forming] 5 (Hepaticflavin-containing monooxygenase 5) (FMO 5) (Dimethylaniline oxidase5); (1692:) dimethylarginine dimethylaminohydrolase 1 [Homo sapiens]; (1693:) dimethylarginine dimethylaminohydrolase 2 [Homo sapiens]; (1694:) dimethylglycine dehydrogenase precursor [Homo sapiens]; (1695:) DIP2 disco-interacting protein 2 homolog B [Homo sapiens]; (1696:) DIP2 disco-interacting protein 2 homolog C (Drosophila) [Homosapiens]; (1697:) DIP2 disco-interacting protein 2 homolog C [Homo sapiens]; (1698:) DIP2B protein [Homo sapiens]; (1699:) DIP2C protein [Homo sapiens]; (1700:) DIP2-like protein isoform a [Homo sapiens]; (1701:) dipeptidase 1 (renal) [Homo sapiens]; (1702:) Dipeptidase 1 precursor (Microsomal dipeptidase) (Renaldipeptidase) (hRDP) (Dehydropeptidase-I); (1703:) Dipeptidase 2 precursor; (1704:) Dipeptidase 3 precursor; (1705:) dipeptidyl peptidase 7 preproprotein [Homo sapiens]; (1706:) Dipeptidyl peptidase 8 (Dipeptidyl peptidase VIII) (DP8) (Prolyldipeptidase DPP8) (Dipeptidyl peptidase IV-related protein 1)(DPRP-1); (1707:) dipeptidyl peptidase 8 [Homo sapiens]; (1708:) dipeptidyl peptidase 8 isoform 1 [Homo sapiens]; (1709:) dipeptidyl peptidase 8 isoform 2 [Homo sapiens]; (1710:) dipeptidyl peptidase 8 isoform 3 [Homo sapiens]; (1711:) dipeptidyl peptidase 8 isoform 4 [Homo sapiens]; (1712:) Dipeptidyl peptidase 9 (Dipeptidyl peptidase IX) (DP9) (Dipeptidylpeptidase-like protein 9) (DPLP9) (Dipeptidyl peptidase IV-relatedprotein 2) (DPRP-2); (1713:) dipeptidyl peptidase III [Homo sapiens]; (1714:) dipeptidylpeptidase 9 [Homo sapiens]; (1715:) dipeptidylpeptidase IV [Homo sapiens]; (1716:) Diphosphoinositol polyphosphate phosphohydrolase 1 (DIPP-1)(Diadenosine 5',5'''-P1,P6-hexaphosphate hydrolase 1) (Nucleosidediphosphate-linked moiety X motif 3) (Nudix motif 3); (1717:) Diphosphoinositol polyphosphate phosphohydrolase 2 (DIPP-2)(Diadenosine 5',5'''-P1,P6-hexaphosphate hydrolase 2) (Nucleosidediphosphate-linked moiety X motif 4) (Nudix motif 4); (1718:) Diphosphoinositol polyphosphate phosphohydrolase 3 alpha (DIPP-3alpha) (DIPP3 alpha) (hDIPP3alpha) (Diadenosine5',5'''-P1,P6-hexaphosphate hydrolase 3 alpha) (Nucleosidediphosphate-linked moiety X motif 10) (Nudix motif 10) (hAps2); (1719:) Diphosphoinositol polyphosphate phosphohydrolase 3 beta (DIPP-3beta) (DIPP3 beta) (hDIPP3beta) (Diadenosine5',5'''-P1,P6-hexaphosphate hydrolase 3 beta) (Nucleosidediphosphate-linked moiety X motif 11) (Nudix motif 11) (hAps1); (1720:)

diphosphomevalonate decarboxylase [Homo sapiens]; (1721:) Discoidin domain-containing receptor 2 precursor (Discoidin domainreceptor 2) (Receptor protein-tyrosine kinase TKT)(Tyrosine-protein kinase TYRO 10) (Neurotrophic tyrosine kinase,receptor-related 3) (CD167b antigen); (1722:) Disco-interacting protein 2 homolog A; (1723:) Disco-interacting protein 2 homolog C; (1724:) DLST [Homo sapiens]; (1725:) DNA (cytosine-5-)-methyltransferase 1 [Homo sapiens]; (1726:) DNA cytosine methyltransferase 3 alpha isoform a [Homo sapiens]; (1727:) DNA cytosine methyltransferase 3 alpha isoform b [Homo sapiens]; (1728:) DNA cytosine methyltransferase 3 alpha isoform c [Homo sapiens]; (1729:) DNA cytosine-5 methyltransferase 3 beta isoform 1 [Homo sapiens]; (1730:) DNA cytosine-5 methyltransferase 3 beta isoform 2 [Homo sapiens]; (1731:) DNA cytosine-5 methyltransferase 3 beta isoform 3 [Homo sapiens]; (1732:) DNA cytosine-5 methyltransferase 3 beta isoform 6 [Homo sapiens]; (1733:) DNA dC->dU-editing enzyme APOBEC-3F (Apolipoprotein B mRNA-editingenzyme catalytic polypeptide-like 3F); (1734:) DNA dC->dU-editing enzyme APOBEC-3G (APOBEC-related cytidinedeaminase) (ARCD) (APOBEC-related protein) (ARP-9) (CEM15)(CEM-15); (1735:) DNA directed RNA polymerase II polypeptide A [Homo sapiens]; (1736:) DNA directed RNA polymerase II polypeptide B [Homo sapiens]; (1737:) DNA fragmentation factor subunit beta (DNA fragmentation factor 40kDa subunit) (DFF-40) (Caspase-activated deoxyribonuclease)(Caspase-activated DNase) (CAD) (Caspase-activated nuclease)(CPAN); (1738:) DNA helicase II, HDH II=ATP-dependent DNA unwinding enzyme/Kuautoantigen large subunit {N-terminal} [human, HeLa cells, PeptidePartial, 19 aa]; (1739:) DNA ligase 3 (DNA ligase III) (Polydeoxyribonucleotide synthase[ATP] 3); (1740:) DNA ligase 4 (DNA ligase IV) (Polydeoxyribonucleotide synthase[ATP] 4); (1741:) DNA ligase I [Homo sapiens]; (1742:) DNA ligase III [Homo sapiens]; (1743:) DNA ligase IV [Homo sapiens]; (1744:) DNA mismatch repair protein [Homo sapiens]; (1745:) DNA mismatch repair protein homolog [Homo sapiens]; (1746:) DNA mismatch repair protein Mlh1 (MutL protein homolog 1); (1747:) DNA mismatch repair protein Mlh3 (MutL protein homolog 3); (1748:) DNA mismatch repair protein MLH3 [Homo sapiens]; (1749:) DNA mismatch repair protein; (1750:) DNA nucleotidylexotransferase (Terminal addition enzyme) (Terminaldeoxynucleotidyltransferase) (Terminal transferase); (1751:) DNA polymerase beta; (1752:) DNA polymerase beta2 [Homo sapiens]; (1753:) DNA polymerase epsilon, catalytic subunit A (DNA polymerase IIsubunit A); (1754:) DNA polymerase lambda (Pol Lambda) (DNA polymerase kappa) (DNApolymerase beta-2) (Pol beta2); (1755:) DNA polymerase subunit alpha B

(DNA polymerase alpha 70 kDasubunit); (1756:) DNA polymerase subunit gamma 2, mitochondrial precursor(Mitochondrial DNA polymerase accessory subunit) (PolG-beta)(MtPolB) (DNA polymerase gamma accessory 55 kDa subunit) (p55); (1757:) DNA polymerase theta [Homo sapiens]; (1758:) DNA primase large subunit, 58kDa [Homo sapiens]; (1759:) DNA primase small subunit, 49kDa [Homo sapiens]; (1760:) DNA repair enzyme; (1761:) DNA replication licensing factor MCM6 (p105MCM); (1762:) DNA topoisomerase 1 (DNA topoisomerase I); (1763:) DNA topoisomerase 2-alpha (DNA topoisomerase II, alpha isozyme); (1764:) DNA topoisomerase I [Homo sapiens]; (1765:) DNA topoisomerase I, mitochondrial precursor (TOP1mt); (1766:) DNA topoisomerase II [Homo sapiens]; (1767:) DNA topoisomerase II, alpha isozyme [Homo sapiens]; (1768:) DNA topoisomerase II, beta isozyme [Homo sapiens]; (1769:) DNA-(apurinic or apyrimidinic site) lyase (AP endonuclease 1) (APEXnuclease) (APEN) (REF-1 protein); (1770:) DNA-3-methyladenine glycosylase (3-methyladenine DNA glycosidase)(ADPG) (3-alkyladenine DNA glycosylase) (N-methylpurine-DNAglycosylase); (1771:) DNA-binding protein [Homo sapiens]; (1772:) DNA-dependent protein kinase catalytic subunit (DNA-PK catalyticsubunit) (DNA-PKcs) (DNPK1) (p460); (1773:) DNA-directed RNA polymerase II 19 kDa polypeptide (RPB7); (1774:) DNA-directed RNA polymerase III largest subunit (RPC155) (RPC1); (1775:) DNA-directed RNA polymerase III subunit C (DNA-directed III 62 kDapolypeptide) (RNA polymerase III C62 subunit) (RPC3); (1776:) DnaJ (Hsp40) homolog, subfamily B, member 6 isoform a [Homosapiens]; (1777:) DnaJ (Hsp40) homolog, subfamily B, member 6 isoform b [Homosapiens]; (1778:) docking protein 1 [Homo sapiens]; (1779:) dodecenoyl-CoA delta-isomerase [Homo sapiens]; (1780:) dodecenoyl-Coenzyme A delta isomerase precursor [Homo sapiens]; (1781:) dolichol monophosphate mannose synthase [Homo sapiens]; (1782:) Dolichol-phosphate mannosyltransferase (Dolichol-phosphate mannosesynthase) (Dolichyl-phosphate beta-D-mannosyltransferase)(Mannose-P-dolichol synthase) (MPD synthase) (DPM synthase); (1783:) Dolichyl-diphosphooligosaccharide--protein glycosyltransferase 48kDa subunit precursor (Oligosaccharyl transferase 48 kDa subunit)(DDOST 48 kDa subunit); (1784:) Dolichyl-diphosphooligosaccharide--protein glycosyltransferase 63kDa subunit precursor (Ribophorin II) (RPN-II) (RIBIIR); (1785:) Dolichyl-diphosphooligosaccharide--protein glycosyltransferase 67kDa subunit precursor (Ribophorin I) (RPN-I); (1786:) Dolichyl-diphosphooligosaccharide--protein glycosyltransferasesubunit DAD1 (Oligosaccharyl transferase subunit DAD1) (Defenderagainst cell death 1) (DAD-1);

(1787:) Dolichyl-diphosphooligosaccharide--protein glycosyltransferasesubunit STT3A (Oligosaccharyl transferase subunit STT3A) (STT3-A)(B5) (Integral membrane protein 1) (TMC); (1788:) Dolichyl-diphosphooligosaccharide--protein glycosyltransferasesubunit STT3B (Oligosaccharyl transferase subunit STT3B) (STT3-B)(Source of immunodominant MHC-associated peptides homolog); (1789:) dolichyl-phosphate mannosyltransferase polypeptide 1 [Homosapiens]; (1790:) dolichyl-phosphate mannosyltransferase polypeptide 2, regulatorysubunit [Homo sapiens]; (1791:) dolichyl-phosphate mannosyltransferase polypeptide 3 isoform 1[Homo sapiens]; (1792:) dolichyl-phosphate mannosyltransferase polypeptide 3 isoform 2[Homo sapiens]; (1793:) DOLPP1 protein [Homo sapiens]; (1794:) dopa decarboxylase (aromatic L-amino acid decarboxylase) [Homosapiens]; (1795:) dopachrome tautomerase (dopachrome delta-isomerase,tyrosine-related protein 2) [Homo sapiens]; (1796:) Dopamine beta-hydroxylase precursor (Dopamine beta-monooxygenase); (1797:) dopamine beta-hydroxylase precursor [Homo sapiens]; (1798:) double-stranded RNA adenosine deaminase; (1799:) Double-stranded RNA-specific adenosine deaminase (DRADA) (136 kDadouble-stranded RNA-binding protein) (P136) (K88DSRBP)(Interferon-inducible protein 4) (IFI-4 protein); (1800:) Double-stranded RNA-specific editase 1 (dsRNA adenosine deaminase)(RNA-editing deaminase 1) (RNA-editing enzyme 1); (1801:) Double-stranded RNA-specific editase B2 (dsRNA adenosine deaminaseB2) (RNA-dependent adenosine deaminase 3) (RNA-editing deaminase 2)(RNA-editing enzyme 2); (1802:) Drug-Protein Interactions:) Structure Of Sulfonamide Drug ComplexedWith Human Carbonic Anhydrase I; (1803:) dsRNA adenosine deaminase DRADA2a [Homo sapiens]; (1804:) dsRNA adenosine deaminase DRADA2b [Homo sapiens]; (1805:) dsRNA adenosine deaminase DRADA2c [Homo sapiens]; (1806:) Dual 3',5'-cyclic-AMP and -GMP phosphodiesterase 11A (cAMP and cGMPphosphodiesterase 11A); (1807:) Dual oxidase 1 precursor (NADPH thyroid oxidase 1) (Thyroid oxidase1) (Large NOX 1) (Long NOX 1); (1808:) Dual oxidase 2 precursor (NADPH oxidase/peroxidase DUOX2) (NADPHthyroid oxidase 2) (Thyroid oxidase 2) (NADH/NADPH thyroid oxidasep138-tox) (p138 thyroid oxidase) (Large NOX 2) (Long NOX 2); (1809:) Dual specificity mitogen-activated protein kinase kinase 1 (MAPkinase kinase 1) (MAPKK 1) (ERK activator kinase 1) (MAPK/ERKkinase 1) (MEK1); (1810:) Dual specificity mitogen-activated protein kinase kinase 3 (MAPkinase kinase 3) (MAPKK 3) (MAPK/ERK kinase 3); (1811:) Dual specificity mitogen-activated protein kinase kinase 6 (MAPkinase kinase 6) (MAPKK 6) (MAPK/ERK kinase 6) (SAPKK3); (1812:) Dual specificity protein phosphatase 18

(Low molecular weight dualspecificity phosphatase 20); (1813:) Dual specificity protein phosphatase 23 (Low molecular mass dualspecificity phosphatase 3) (LDP-3) (VH1-like phosphatase Z); (1814:) Dual specificity testis-specific protein kinase 1 (Testicularprotein kinase 1); (1815:) Dual specificity testis-specific protein kinase 2 (Testicularprotein kinase 2); (1816:) Dual specificity tyrosine-phosphorylation-regulated kinase 1A(Protein kinase minibrain homolog) (MNBH) (HP86) (Dual specificityYAK1-related kinase); (1817:) Dual specificity tyrosine-phosphorylation-regulated kinase 1B (Mirkprotein kinase) (Minibrain-related kinase); (1818:) Dual specificity tyrosine-phosphorylation-regulated kinase 2; (1819:) Duffy antigen/chemokine receptor (Fy glycoprotein) (GpFy)(Glycoprotein D) (Plasmodium vivax receptor) (CD234 antigen); (1820:) dUTP pyrophosphatase isoform 1 precursor [Homo sapiens]; (1821:) dUTP pyrophosphatase isoform 2 [Homo sapiens]; (1822:) dUTP pyrophosphatase isoform 3 [Homo sapiens]; (1823:) dUTP pyrophosphatase; (1824:) dynamin 1 isoform 1 [Homo sapiens]; (1825:) dynamin 1 isoform 2 [Homo sapiens]; (1826:) Dynamin-1-like protein (Dynamin-like protein) (Dnm1p/Vps1p-likeprotein) (DVLP) (Dynamin family member proline-richcarboxyl-terminal domain less) (Dymple) (Dynamin-related protein 1)(Dynamin-like protein 4) (Dynamin-like protein IV) (HdynIV); (1827:) dynein light chain 1 [Homo sapiens]; (1828:) dystonin isoform 1 [Homo sapiens]; (1829:) dystonin isoform 1e precursor [Homo sapiens]; (1830:) dystonin isoform 1eA precursor [Homo sapiens]; (1831:) dystonin isoform 1eB precursor [Homo sapiens]; (1832:) E-1 enzyme [Homo sapiens]; (1833:) E1A binding protein p300 [Homo sapiens]; (1834:) E1A-associated protein p300; (1835:) E2 protein [Homo sapiens]; (1836:) E2 ubiquitin-conjugating enzyme [Homo sapiens]; (1837:) E2F transcription factor 2 [Homo sapiens]; (1838:) E3 ubiquitin ligase IBRDC2 (IBR domain-containing protein 2)(p53-inducible RING finger protein); (1839:) E3 ubiquitin ligase TRIAD3 (Ubiquitin-conjugating enzyme7-interacting protein 1) (Zinc finger protein inhibitingNF-kappa-B) (Triad domain-containing protein 3); (1840:) E3 ubiquitin protein ligase TRAF7 (TNF receptor-associated factor7) (RING finger and WD repeat domain protein 1) (RING fingerprotein 119); (1841:) E3 ubiquitin-protein ligase CBL (Signal transduction protein CBL)(Proto-oncogene c-CBL) (Casitas B-lineage lymphoma proto-oncogene)(RING finger protein 55); (1842:) E3 ubiquitin-protein ligase CBL-B (Signal transduction proteinCBL-B) (SH3-binding protein CBL-B) (Casitas B-lineage lymphomaproto-oncogene b) (RING finger protein 56); (1843:) E3 ubiquitin-protein ligase HECTD1 (HECT domain-containing protein1) (E3 ligase for inhibin receptor) (EULIR); (1844:) E3 ubiquitin-protein ligase NEDD4; (1845:) E3 ubiquitin-protein

ligase NEDD4-like protein (Nedd4-2) (NEDD4.2); (1846:) early growth response 1 [Homo sapiens]; (1847:) EBV-induced G-protein coupled receptor 2 (EBI2); (1848:) ECE-1 [Homo sapiens]; (1849:) ectonucleoside triphosphate diphosphohydrolase 2 isoform 1 [Homosapiens]; (1850:) ectonucleoside triphosphate diphosphohydrolase 2 isoform 2 [Homosapiens]; (1851:) "Ectonucleotide pyrophosphatase/phosphodiesterase 1 (E-NPP 1)(Phosphodiesterase I/nucleotide pyrophosphatase 1) (Plasma-cellmembrane glycoprotein PC-1) [Includes:) Alkaline phosphodiesterase I; Nucleotide pyrophosphatase (NPPase)]."; (1852:) Ectonucleotide pyrophosphatase/phosphodiesterase 6 precursor(E-NPP6) (NPP-6) [Contains:) Ectonucleotidepyrophosphatase/phosphodiesterase 6 soluble form]; (1853:) ectonucleotide pyrophosphatase/phosphodiesterase 7 [Homo sapiens]; (1854:) Ectonucleotide pyrophosphatase/phosphodiesterase 7 precursor(E-NPP7) (NPP-7) (Alkaline sphingomyelin phosphodiesterase)(Intestinal alkaline sphingomyelinase) (Alk-SMase); (1855:) EGF, latrophilin and seven transmembrane domain-containing protein1 precursor (EGF-TM7-latrophilin-related protein) (ETL protein); (1856:) EGF-like module-containing mucin-like hormone receptor-like 1precursor (Cell surface glycoprotein EMR1) (EMR1 hormone receptor); (1857:) EGF-like module-containing mucin-like hormone receptor-like 2precursor (EGF-like module EMR2) (CD312 antigen); (1858:) EGF-like module-containing mucin-like hormone receptor-like 3precursor (EGF-like module-containing mucin-like receptor EMR3); (1859:) EGF-like module-containing mucin-like hormone receptor-like 4precursor (G-protein coupled receptor 127); (1860:) EGL nine (C.elegans) homolog 2 isoform 1 [Homo sapiens]; (1861:) EGL nine (C.elegans) homolog 2 isoform 2 [Homo sapiens]; (1862:) EGL nine (C.elegans) homolog 2 isoform 3 [Homo sapiens]; (1863:) Egl nine homolog 1 (Hypoxia-inducible factor prolyl hydroxylase 2)(HIF-prolyl hydroxylase 2) (HIF-PH2) (HPH-2) (Prolyl hydroxylasedomain-containing protein 2) (PHD2) (SM-20); (1864:) Egl nine homolog 3 (Hypoxia-inducible factor prolyl hydroxylase 3)(HIF-prolyl hydroxylase 3) (HIF-PH3) (HPH-1) (Prolyl hydroxylasedomain-containing protein 3) (PHD3); (1865:) elastase 1, pancreatic [Homo sapiens]; (1866:) elastase 2, neutrophil preproprotein [Homo sapiens]; (1867:) elastase isozyme 4, HSE I-4 [human, sputum, Peptide Partial, 21aa]; (1868:) ELAV-like 1 [Homo sapiens]; (1869:) Electrogenic sodium bicarbonate cotransporter 1 (Sodium bicarbonatecotransporter) (Na(+)/HCO3(-) cotransporter) (Solute carrier family4 member 4) (kNBC1); (1870:) Elongation factor 2 kinase (eEF-2 kinase) (eEF-2K)(Calcium/calmodulin-dependent eukaryotic elongation factor 2kinase); (1871:) elongin B [Homo sapiens]; (1872:) elongin B

isoform a [Homo sapiens]; (1873:) elongin B isoform b [Homo sapiens]; (1874:) elongin C [Homo sapiens]; (1875:) endo-beta-N-acetylglucosaminidase [Homo sapiens]; (1876:) endonuclease III [Homo sapiens]; (1877:) Endonuclease III-like protein 1; (1878:) Endonuclease VIII-like 2 (Nei-like 2) (DNA glycosylase/AP lyaseNeil2) (DNA-(apurinic or apyrimidinic site) lyase Neil2) (NEH2); (1879:) endopeptidase La homolog (EC 3.4.21.-) precursor, mitochondrial(version 2) - human; (1880:) endoplasmic reticulum alpha-mannosidase I [Homo sapiens]; (1881:) Endoplasmic reticulum mannosyl-oligosaccharide1,2-alpha-mannosidase (ER alpha-1,2-mannosidase) (Mannosidase alphaclass 1B member 1) (Man9GlcNAc2-specific-processingalpha-mannosidase); (1882:) endothelial cell growth factor 1 (platelet-derived) [Homo sapiens]; (1883:) Endothelial cells scavenger receptor precursor (Acetyl LDLreceptor) (Scavenger receptor class F member 1); (1884:) Endothelial lipase precursor (Endothelial cell-derived lipase)(EDL) (EL); (1885:) Endothelial protein C receptor precursor (Endothelial cell proteinC receptor) (Activated protein C receptor) (APC receptor) (CD201antigen); (1886:) endothelin 1 [Homo sapiens]; (1887:) endothelin 3 isoform 1 preproprotein [Homo sapiens]; (1888:) endothelin 3 isoform 2 preproprotein [Homo sapiens]; (1889:) endothelin 3 isoform 3 preproprotein [Homo sapiens]; (1890:) Endothelin B receptor precursor (ET-B) (Endothelin receptorNon-selective type); (1891:) Endothelin B receptor-like protein 2 precursor (ETBR-LP-2)(G-protein coupled receptor 37-like 1); (1892:) endothelin converting enzyme [Homo sapiens]; (1893:) endothelin converting enzyme 1 [Homo sapiens]; (1894:) endothelin converting enzyme 1 isoform 1c [Homo sapiens]; (1895:) endothelin converting enzyme 2 isoform A [Homo sapiens]; (1896:) endothelin converting enzyme 2 isoform B [Homo sapiens]; (1897:) endothelin converting enzyme-1 [Homo sapiens]; (1898:) endothelin converting enzyme-2A [Homo sapiens]; (1899:) endothelin converting enzyme-2B [Homo sapiens]; (1900:) endothelin converting enzyme-like 1 [Homo sapiens]; (1901:) endothelin receptor type A [Homo sapiens]; (1902:) endothelin receptor type B isoform 1 [Homo sapiens]; (1903:) endothelin receptor type B isoform 2 [Homo sapiens]; (1904:) Endothelin-1 receptor precursor (Endothelin A receptor) (ET-A)(hET-AR) (ETA-R); (1905:) endothelin-converting enzyme [Homo sapiens]; (1906:) Endothelin-converting enzyme 1 (ECE-1); (1907:) Endothelin-converting enzyme 2 (ECE-2); (1908:) endothelin-converting enzyme 2B [Homo sapiens]; (1909:) endothelin-converting enzyme, isoform ECE-1a [Homo sapiens]; (1910:) endothelin-converting enzyme, isoform ECE-1b [Homo sapiens]; (1911:) endothelin-converting enzyme; (1912:) endothelin-converting enzyme-1c [Homo

sapiens]; (1913:) endothelin-converting enzyme-2C [Homo sapiens]; (1914:) Endothelin-converting enzyme-like 1 (Xce protein); (1915:) endothelin-converting-enzyme 1 [Homo sapiens]; (1916:) endotheline-converting enzyme ECEL1 [Homo sapiens]; (1917:) enolase 1 [Homo sapiens]; (1918:) enolase 2 [Homo sapiens]; (1919:) enolase 3 [Homo sapiens]; (1920:) enoyl-CoA hydratase:) 3-hydroxyacyl-CoA dehydrogenase; (1921:) enoyl-Coenzyme A, hydratase/3-hydroxyacyl Coenzyme A dehydrogenase[Homo sapiens]; (1922:) enterocyte differentiation associated factor EDAF-1 [Homo sapiens]; (1923:) enterokinase precursor [Homo sapiens]; (1924:) enyol-CoA:) hydratase/3-hydroxyacyl-CoA dehydrogenase; (1925:) eosinophil serine protease [Homo sapiens]; (1926:) eosinophil serine protease 1 splicing variant [Homo sapiens]; (1927:) ephrin receptor EphB2 isoform 1 precursor [Homo sapiens]; (1928:) ephrin receptor EphB2 isoform 2 precursor [Homo sapiens]; (1929:) Ephrin type-A receptor 1 precursor (Tyrosine-protein kinasereceptor EPH); (1930:) Ephrin type-A receptor 10 precursor; (1931:) Ephrin type-A receptor 2 precursor (Tyrosine-protein kinasereceptor ECK) (Epithelial cell kinase); (1932:) Ephrin type-A receptor 3 precursor (Tyrosine-protein kinasereceptor ETK1) (HEK) (HEK4); (1933:) Ephrin type-A receptor 4 precursor (Tyrosine-protein kinasereceptor SEK) (Receptor protein-tyrosine kinase HEK8); (1934:) Ephrin type-A receptor 5 precursor (Tyrosine-protein kinasereceptor EHK-1) (EPH homology kinase 1) (Receptor protein-tyrosinekinase HEK7); (1935:) Ephrin type-A receptor 6 precursor (Tyrosine-protein kinasereceptor EHK-2) (EPH homology kinase 2); (1936:) Ephrin type-A receptor 7 precursor (Tyrosine-protein kinasereceptor EHK-3) (EPH homology kinase 3) (Receptor protein-tyrosinekinase HEK11); (1937:) Ephrin type-A receptor 8 precursor (Tyrosine-protein kinasereceptor EEK) (EPH- and ELK-related kinase) (HEK3); (1938:) Ephrin type-B receptor 1 precursor (Tyrosine-protein kinasereceptor EPH-2) (NET) (HEK6) (ELK); (1939:) Ephrin type-B receptor 2 precursor (Tyrosine-protein kinasereceptor EPH-3) (DRT) (Receptor protein-tyrosine kinase HEK5) (ERK)(NY-REN-47 antigen); (1940:) Ephrin type-B receptor 3 precursor (Tyrosine-protein kinasereceptor HEK-2); (1941:) Ephrin type-B receptor 4 precursor (Tyrosine-protein kinasereceptor HTK); (1942:) Ephrin type-B receptor 6 precursor (Tyrosine-proteinkinase-defective receptor EPH-6) (HEP); (1943:) epidermal growth factor (beta-urogastrone) [Homo sapiens]; (1944:) epidermal growth factor receptor isoform a [Homo sapiens]; (1945:) epidermal growth factor receptor isoform b [Homo sapiens]; (1946:) epidermal growth factor receptor isoform c [Homo sapiens]; (1947:) epidermal growth factor receptor isoform d [Homo sapiens]; (1948:) epidermal growth factor receptor pathway substrate 15

[Homosapiens]; (1949:) Epidermal growth factor receptor precursor (Receptortyrosine-protein kinase ErbB-1); (1950:) Epithelial discoidin domain-containing receptor 1 precursor(Epithelial discoidin domain receptor 1) (Tyrosine kinase DDR)(Discoidin receptor tyrosine kinase) (Tyrosine-protein kinase CAK)(Cell adhesion kinase) (TRK E) (Protein-tyrosine kinase RTK 6)(HGK2) (CD167a antigen); (1951:) Epoxide hydrolase 1 (Microsomal epoxide hydrolase) (Epoxidehydratase); (1952:) Epoxide hydrolase 2 (Soluble epoxide hydrolase) (SEH) (Epoxidehydratase) (Cytosolic epoxide hydrolase) (CEH); (1953:) epoxide hydrolase 2, cytoplasmic [Homo sapiens]; (1954:) epsilon isoform of regulatory subunit B56, protein phosphatase 2A[Homo sapiens]; (1955:) epsilon-trimethyllysine 2-oxoglutarate dioxygenase [Homo sapiens]; (1956:) ER lumen protein retaining receptor 1 (KDEL receptor 1) (KDELendoplasmic reticulum protein retention receptor 1) (PutativeMAPK-activating protein PM23); (1957:) ER lumen protein retaining receptor 2 (KDEL receptor 2) (KDELendoplasmic reticulum protein retention receptor 2) (ERD2-likeprotein 1) (ELP-1); (1958:) ER lumen protein retaining receptor 3 (KDEL receptor 3) (KDELendoplasmic reticulum protein retention receptor 3); (1959:) ERO1-like protein alpha precursor (ERO1-Lalpha)(Oxidoreductin-1-Lalpha) (Endoplasmic oxidoreductin-1-like protein)(ERO1-L); (1960:) ERO1-like protein beta precursor (ERO1-Lbeta)(Oxidoreductin-1-Lbeta) (Endoplasmic oxidoreductin-1-like proteinB); (1961:) erythrocyte acylphosphatase 1 isoform a [Homo sapiens]; (1962:) erythrocyte acylphosphatase 1 isoform b [Homo sapiens]; (1963:) erythrocyte adenosine monophosphate deaminase isoform 1A [Homosapiens]; (1964:) erythrocyte adenosine monophosphate deaminase isoform 1B [Homosapiens]; (1965:) erythrocyte adenosine monophosphate deaminase isoform 1C [Homosapiens]; (1966:) Erythropoietin receptor precursor (EPO-R); (1967:) estradiol 17 beta-dehydrogenase 8 [Homo sapiens]; (1968:) Estradiol 17-beta-dehydrogenase 1 (17-beta-hydroxysteroiddehydrogenase type 1) (17-beta-HSD 1) (Placental17-beta-hydroxysteroid dehydrogenase) (20 alpha-hydroxysteroiddehydrogenase) (20-alpha-HSD) (E2DH); (1969:) Estradiol 17-beta-dehydrogenase 12 (17-beta-HSD 12)(17-beta-hydroxysteroid dehydrogenase 12) (3-ketoacyl-CoAreductase) (KAR); (1970:) Estradiol 17-beta-dehydrogenase 2 (17-beta-HSD 2) (Microsomal17-beta-hydroxysteroid dehydrogenase) (20 alpha-hydroxysteroiddehydrogenase) (20-alpha-HSD) (E2DH); (1971:) Estrogen receptor (ER) (Estradiol receptor) (ER-alpha); (1972:) Estrogen receptor beta (ER-beta); (1973:) estrogen-related receptor alpha [Homo sapiens]; (1974:) Estrogen-related receptor gamma (Estrogen receptor-related protein3) (ERR gamma-2); (1975:)

ethanolamine kinase 1 isoform A [Homo sapiens]; (1976:) ethanolamine kinase 1 isoform B [Homo sapiens]; (1977:) ets variant gene 6 [Homo sapiens]; (1978:) Eukaryotic translation initiation factor 2-alpha kinase 1(Heme-regulated eukaryotic initiation factor eIF-2-alpha kinase)(Heme-regulated inhibitor) (Heme-controlled repressor) (HCR)(Hemin-sensitive initiation factor 2-alpha kinase); (1979:) eukaryotic translation initiation factor 2-alpha kinase 2 [Homosapiens]; (1980:) Eukaryotic translation initiation factor 2-alpha kinase 3 precursor(PRKR-like endoplasmic reticulum kinase) (Pancreatic eIF2-alphakinase) (HsPEK); (1981:) Eukaryotic translation initiation factor 4 gamma 2 (eIF-4-gamma 2)(eIF-4G 2) (eIF4G 2) (p97) (Death-associated protein 5) (DAP-5); (1982:) evolutionarily related interleukin-1beta converting enzyme [Homosapiens]; (1983:) Exostosin-like 2 (Glucuronyl-galactosyl-proteoglycan4-alpha-N-acetylglucosaminyltransferase)(Alpha-1,4-N-acetylhexosaminyltransferase EXTL2) (Alpha-GalNAcTEXTL2) (EXT-related protein 2); (1984:) Extracellular calcium-sensing receptor precursor (CaSR)(Parathyroid Cell calcium-sensing receptor); (1985:) FAD synthetase isoform 1 [Homo sapiens]; (1986:) FAD1 flavin adenine dinucleotide synthetase homolog (S. cerevisiae)[Homo sapiens]; (1987:) FADD-homologous ICE/CED-3-like protease [Homo sapiens]; (1988:) FAD-synthetase (PP591) [Homo sapiens]; (1989:) FAD-synthetase [Homo sapiens]; (1990:) FAM80B protein [Homo sapiens]; (1991:) Family with sequence similarity 80, member A [Homo sapiens]; (1992:) Family with sequence similarity 80, member B [Homo sapiens]; (1993:) Fanconi anemia complementation group D2 isoform a [Homo sapiens]; (1994:) Fanconi anemia complementation group D2 isoform b [Homo sapiens]; (1995:) Fanconi anemia group D2 protein (Protein FACD2); (1996:) Fanconi anemia, complementation group G [Homo sapiens]; (1997:) Far upstream element-binding protein 2 (FUSE-binding protein 2) (KHtype-splicing regulatory protein) (KSRP) (p75); (1998:) farnesyl diphosphate synthase [Homo sapiens]; (1999:) farnesylated-proteins converting enzyme 1 [Homo sapiens]; (2000:) farnesylated-proteins converting enzyme 2 [Homo sapiens]; (2001:) farnesyl-diphosphate farnesyltransferase 1 [Homo sapiens]; (2002:) Fas-associated death domain protein interleukin-1b-convertingenzyme 2 [Homo sapiens]; (2003:) Fas-associated via death domain [Homo sapiens]; (2004:) fatty acid amide hydrolase [Homo sapiens]; (2005:) fatty acid CoA ligase-like AMP-binding enzyme [Homo sapiens]; (2006:) fatty acid coenzyme A ligase 5 [Homo sapiens]; (2007:) fatty acid desaturase 2 [Homo sapiens]; (2008:) fatty acid omega-hydroxylase (cytochrome P450 4A); (2009:) fatty acid synthase [Homo sapiens]; (2010:) fatty-acid-Coenzyme

A ligase, long-chain 5 [Homo sapiens]; (2011:) FBP2 [Homo sapiens]; (2012:) Fc receptor-like protein 2 precursor (SH2 domain-containingphosphatase anchor protein 1) (Fc receptor homolog 2) (FcRH2)(Immunoglobulin receptor translocation-associated 4 protein); (2013:) Fc receptor-like protein 5 precursor (Immunoglobulin receptortranslocation-associated gene 2 protein) (BXMAS1) (CD307 antigen); (2014:) Feline leukemia virus subgroup C receptor-related protein 1 (Felineleukemia virus subgroup C receptor) (hFLVCR); (2015:) ferredoxin 1 precursor [Homo sapiens]; (2016:) ferredoxin reductase isoform 1 precursor [Homo sapiens]; (2017:) ferredoxin reductase isoform 2 precursor [Homo sapiens]; (2018:) Ferrochelatase (protoporphyria) [Homo sapiens]; (2019:) ferrochelatase [Homo sapiens]; (2020:) ferrochelatase isoform a precursor [Homo sapiens]; (2021:) ferrochelatase isoform b precursor [Homo sapiens]; (2022:) ferrochelatase precursor [Homo sapiens]; (2023:) Ferrochelatase, mitochondrial precursor (Protoheme ferro-lyase)(Heme synthetase); (2024:) fibrinogen, alpha polypeptide isoform alpha preproprotein [Homosapiens]; (2025:) fibrinogen, alpha polypeptide isoform alpha-E preproprotein [Homosapiens]; (2026:) fibroblast activation protein, alpha subunit [Homo sapiens]; (2027:) fibroblast growth factor 23 precursor [Homo sapiens]; (2028:) Fibroblast growth factor receptor 2 precursor (FGFR-2)(Keratinocyte growth factor receptor 2) (CD332 antigen); (2029:) Fibroblast growth factor receptor 3 precursor (FGFR-3) (CD333antigen); (2030:) Fibroblast growth factor receptor 4 precursor (FGFR-4) (CD334antigen); (2031:) Fibroblast growth factor receptor-like 1 precursor (FGFreceptor-like protein 1) (Fibroblast growth factor receptor 5)(FGFR-like protein) (FGF homologous factor receptor); (2032:) fibronectin 1 isoform 1 preproprotein [Homo sapiens]; (2033:) fibronectin 1 isoform 2 preproprotein [Homo sapiens]; (2034:) fibronectin 1 isoform 3 preproprotein [Homo sapiens]; (2035:) fibronectin 1 isoform 4 preproprotein [Homo sapiens]; (2036:) fibronectin 1 isoform 5 preproprotein [Homo sapiens]; (2037:) fibronectin 1 isoform 6 preproprotein [Homo sapiens]; (2038:) fibronectin 1 isoform 7 preproprotein [Homo sapiens]; (2039:) Fk506 And Rapamycin-Binding Protein (Fkbp12) (Nmr, 20 Structures); (2040:) Fk506 And Rapamycin-Binding Protein (Fkbp12) (Nmr, MinimizedAverage Structure Excluding Electrostatic Interactions); (2041:) Fk506 And Rapamycin-Binding Protein (Fkbp12) (Nmr, MinimizedAverage Structure); (2042:) FK506 binding protein 12-rapamycin associated protein 1 [Homosapiens]; (2043:) FK506 binding protein 5 [Homo sapiens]; (2044:) FK506-binding protein 10 precursor (Peptidyl-prolyl cis-transisomerase) (PPlase) (Rotamase) (65 kDa FK506-binding protein)(FKBP65) (Immunophilin FKBP65); (2045:) FK506-binding protein 1A (Peptidyl-prolyl cis-trans isomerase)(PPlase)

(Rotamase) (12 kDa FKBP) (FKBP-12) (Immunophilin FKBP12); (2046:) FK506-binding protein 1A [Homo sapiens]; (2047:) FK506-binding protein 1B (Peptidyl-prolyl cis-trans isomerase 1B)(PPlase 1B) (Rotamase 1B) (12.6 kDa FKBP) (FKBP-12.6) (ImmunophilinFKBP12.6) (h-FKBP-12); (2048:) FK506-binding protein 1B isoform a [Homo sapiens]; (2049:) FK506-binding protein 1B isoform b [Homo sapiens]; (2050:) FK506-binding protein 2 precursor (Peptidyl-prolyl cis-transisomerase) (PPlase) (Rotamase) (13 kDa FKBP) (FKBP-13); (2051:) FK506-binding protein 3 (Peptidyl-prolyl cis-trans isomerase)(PPlase) (Rotamase) (25 kDa FKBP) (FKBP-25) (Rapamycin-selective 25kDa immunophilin); (2052:) FK506-binding protein 4 [Homo sapiens]; (2053:) FK506-binding protein 5 (Peptidyl-prolyl cis-trans isomerase)(PPlase) (Rotamase) (51 kDa FK506-binding protein) (FKBP-51) (54kDa progesterone receptor-associated immunophilin) (FKBP54) (P54)(FF1 antigen) (HSP90-binding immunophilin) (Androgen-regulatedprotein 6); (2054:) FK506-binding protein 6 [Homo sapiens]; (2055:) FK506-binding protein 9 precursor (Peptidyl-prolyl cis-transisomerase) (PPlase) (Rotamase); (2056:) FL cytokine receptor precursor (Tyrosine-protein kinase receptorFLT3) (Stem cell tyrosine kinase 1) (STK-1) (CD135 antigen); (2057:) FLAD1 protein [Homo sapiens]; (2058:) FLAME-1 [Homo sapiens]; (2059:) FLAME-1-beta [Homo sapiens]; (2060:) FLAME-1-delta [Homo sapiens]; (2061:) FLAME-1-gamma [Homo sapiens]; (2062:) flap structure-specific endonuclease 1 [Homo sapiens]; (2063:) flavin adenine dinucleotide synthetase isoform 1 [Homo sapiens]; (2064:) flavin adenine dinucleotide synthetase isoform 2 [Homo sapiens]; (2065:) flavin containing monooxygenase 1 [Homo sapiens]; (2066:) flavin containing monooxygenase 2 (non-functional) [Homo sapiens]; (2067:) flavin containing monooxygenase 4 [Homo sapiens]; (2068:) flavin containing monooxygenase 5 [Homo sapiens]; (2069:) Flavin reductase (FR) (NADPH-dependent diaphorase) (NADPH-flavinreductase) (FLR) (Biliverdin reductase B) (BVR-B) (Biliverdin-IXbeta-reductase) (Green heme-binding protein) (GHBP); (2070:) FLICE-like inhibitory protein long form [Homo sapiens]; (2071:) FLJ00013 protein [Homo sapiens]; (2072:) FLJ00207 protein [Homo sapiens]; (2073:) FLJ00405 protein [Homo sapiens]; (2074:) FLJ11011 [Homo sapiens]; (2075:) FLJ12389 protein [Homo sapiens]; (2076:) FLJ13855 [Homo sapiens]; (2077:) FLJ20581 protein [Homo sapiens]; (2078:) FLJ21963 protein [Homo sapiens]; (2079:) fMet-Leu-Phe receptor (fMLP receptor) (N-formyl peptide receptor)(FPR) (N-formylpeptide chemoattractant receptor); (2080:) FMLP-related receptor I (FMLP-R-I) (Lipoxin A4 receptor) (LXA4receptor) (Formyl peptide receptor-like 1) (RFP) (HM63); (2081:) FMLP-related receptor II (FMLP-R-II)

(Formylpeptide receptor-like2); (2082:) fms-related tyrosine kinase 1 (vascular endothelial growthfactor/vascular permeability factor receptor) [Homo sapiens]; (2083:) folate hydrolase 1 isoform 1 [Homo sapiens]; (2084:) folate hydrolase 1 isoform 2 [Homo sapiens]; (2085:) Folate receptor alpha precursor (FR-alpha) (Folate receptor 1)(Folate receptor, adult) (Adult folate-binding protein) (FBP)(Ovarian tumor-associated antigen MOv18) (KB cells FBP); (2086:) Folate receptor beta precursor (FR-beta) (Folate receptor 2)(Folate receptor, fetal/placental) (Placental folate-bindingprotein) (FBP); (2087:) Folate receptor gamma precursor (FR-gamma) (Folate receptor 3); (2088:) Follicle-stimulating hormone receptor precursor (FSH-R)(Follitropin receptor); (2089:) folylpolyglutamate synthase isoform a precursor [Homo sapiens]; (2090:) folylpolyglutamate synthase isoform b [Homo sapiens]; (2091:) Folylpolyglutamate synthase, mitochondrial precursor(Folylpoly-gamma-glutamate synthetase) (FPGS) (Tetrahydrofolatesynthase) (Tetrahydrofolylpolyglutamate synthase); (2092:) "Formimidoyltransferase-cyclodeaminase(Formiminotransferase-cyclodeaminase) (FTCD) (LCHC1) [Includes:Glutamate formimidoyltransferase (Glutamate formiminotransferase)(Glutamate formyltransferase); Formimidoyltetrahydrofolatecyclodeaminase (Formiminotetrahydrofolate cyclodeaminase)]."; (2093:) formiminotransferase cyclodeaminase [Homo sapiens]; (2094:) fragile histidine triad gene [Homo sapiens]; (2095:) frataxin isoform 1 preproprotein [Homo sapiens]; (2096:) frataxin isoform 2 preproprotein [Homo sapiens]; (2097:) Free fatty acid receptor 1 (G-protein coupled receptor 40); (2098:) Free fatty acid receptor 2 (G-protein coupled receptor 43); (2099:) Free fatty acid receptor 3 (G-protein coupled receptor 41); (2100:) Frizzled-1 precursor (Fz-1) (hFz1) (FzE1); (2101:) Frizzled-10 precursor (Fz-10) (hFz10) (FzE7); (2102:) Frizzled-2 precursor (Fz-2) (hFz2) (FzE2); (2103:) Frizzled-3 precursor (Fz-3) (hFz3); (2104:) Frizzled-4 precursor (Fz-4) (hFz4) (FzE4); (2105:) Frizzled-5 precursor (Fz-5) (hFz5) (FzE5); (2106:) Frizzled-6 precursor (Fz-6) (hFz6); (2107:) Frizzled-7 precursor (Fz-7) (hFz7) (FzE3); (2108:) Frizzled-8 precursor (Fz-8) (hFz8); (2109:) Frizzled-9 precursor (Fz-9) (hFz9) (FzE6) (CD349 antigen); (2110:) fructosamine 3 kinase [Homo sapiens]; (2111:) fructosamine-3-kinase-related protein [Homo sapiens]; (2112:) fructose-1,6-bisphosphatase [Homo sapiens]; (2113:) Fructose-1,6-bisphosphatase 1 (D-fructose-1,6-bisphosphate1-phosphohydrolase 1) (FBPase 1); (2114:) fructose-1,6-bisphosphatase 1 [Homo sapiens]; (2115:) fructose-1,6-bisphosphatase 1 variant [Homo sapiens]; (2116:) fructose-1,6-bisphosphatase 2 [Homo sapiens]; (2117:) Fructose-1,6-

bisphosphatase isozyme 2 (D-fructose-1,6-bisphosphate1-phosphohydrolase 2) (FBPase 2); (2118:) fructose-1,6-bisphosphatase; (2119:) fructose-6-phosphate,2-kinase/fructose-2, 6-bisphosphatase [Homosapiens]; (2120:) Fructose-bisphosphate aldolase A (Muscle-type aldolase) (Lungcancer antigen NY-LU-1); (2121:) Fructose-bisphosphate aldolase B (Liver-type aldolase); (2122:) Fructose-bisphosphate aldolase C (Brain-type aldolase); (2123:) fructose-bisphosphate aldolase C [Homo sapiens]; (2124:) fucokinase [Homo sapiens]; (2125:) fucose-1-phosphate guanyltransferase [Homo sapiens]; (2126:) Fucose-1-phosphate guanylyltransferase (GDP-L-fucosepyrophosphorylase) (GDP-L-fucose diphosphorylase); (2127:) fucosidase, alpha-L- 1, tissue [Homo sapiens]; (2128:) fucosidase, alpha-L- 2, plasma [Homo sapiens]; (2129:) fucosyltransferase 1 [Homo sapiens]; (2130:) fucosyltransferase 2 (secretor status included) [Homo sapiens]; (2131:) fucosyltransferase 3 (galactoside 3(4)-L-fucosyltransferase, Lewisblood group included) [Homo sapiens]; (2132:) fucosyltransferase 5 [Homo sapiens]; (2133:) fucosyltransferase 8 isoform a [Homo sapiens]; (2134:) fucosyltransferase 8 isoform b [Homo sapiens]; (2135:) fucosyltransferase 8 isoform c [Homo sapiens]; (2136:) fukutin-related protein [Homo sapiens]; (2137:) fumarate hydratase precursor [Homo sapiens]; (2138:) Fumarylacetoacetase (Fumarylacetoacetate hydrolase)(Beta-diketonase) (FAA); (2139:) fumarylacetoacetate hydrolase (fumarylacetoacetase) [Homo sapiens]; (2140:) Furin (paired basic amino acid cleaving enzyme) [Homo sapiens]; (2141:) Furin precursor (Paired basic amino acid residue cleaving enzyme)(PACE) (Dibasic-processing enzyme); (2142:) furin preproprotein [Homo sapiens]; (2143:) Fused toes protein homolog (Ft1); (2144:) FXYD domain containing ion transport regulator 3 isoform 1precursor [Homo sapiens]; (2145:) FXYD domain containing ion transport regulator 3 isoform 2precursor [Homo sapiens]; (2146:) FXYD domain-containing ion transport regulator 2 isoform 1 [Homosapiens]; (2147:) FXYD domain-containing ion transport regulator 2 isoform 2 [Homosapiens]; (2148:) FXYD domain-containing ion transport regulator 5 [Homo sapiens]; (2149:) FXYD domain-containing ion transport regulator 6 [Homo sapiens]; (2150:) FXYD domain-containing ion transport regulator 7 [Homo sapiens]; (2151:) G protein-coupled bile acid receptor 1 [Homo sapiens]; (2152:) G protein-coupled receptor kinase-interactor 2 isoform 1 [Homosapiens]; (2153:) G protein-coupled receptor kinase-interactor 2 isoform 2 [Homosapiens]; (2154:) G protein-coupled receptor kinase-interactor 2 isoform 3 [Homosapiens]; (2155:) G protein-coupled receptor kinase-interactor 2 isoform 4 [Homosapiens]; (2156:) G/T mismatch-specific thymine DNA glycosylase; (2157:) G6b protein precursor; (2158:) GA

binding protein transcription factor, alpha subunit (60kD) [Homosapiens]; (2159:) GABA(A) receptor-associated protein [Homo sapiens]; (2160:) Galactocerebrosidase precursor (GALCERase) (Galactosylceramidase)(Galactosylceramide beta-galactosidase) (Galactocerebrosidebeta-galactosidase); (2161:) Galactokinase (Galactose kinase); (2162:) galactokinase 1 [Homo sapiens]; (2163:) galactose mutarotase (aldose 1-epimerase) [Homo sapiens]; (2164:) galactose-1-phosphate uridyl transferase [Homo sapiens]; (2165:) galactose-1-phosphate uridyl transferase; (2166:) Galactose-1-phosphate uridylyltransferase (Gal-1-Puridylyltransferase) (UDP-glucose--hexose-1-phosphateuridylyltransferase); (2167:) galactose-1-phosphate uridylyltransferase [Homo sapiens]; (2168:) galactose-3-O-sulfotransferase [Homo sapiens]; (2169:) Galactose-3-O-sulfotransferase 2 (Gal3ST-2) (Galbeta1-3GalNAc3'-sulfotransferase 2) (Beta-galactose-3-O-sulfotransferase 2)(Glycoprotein beta-Gal 3'-sulfotransferase 2); (2170:) galactose-3-O-sulfotransferase 2 [Homo sapiens]; (2171:) galactosidase, alpha [Homo sapiens]; (2172:) galactosidase, beta 1 [Homo sapiens]; (2173:) Galactoside 2-alpha-L-fucosyltransferase 1(GDP-L-fucose:beta-D-galactoside 2-alpha-L-fucosyltransferase 1)(Alpha(1,2)FT 1) (Fucosyltransferase 1) (Blood group H alpha2-fucosyltransferase); (2174:) Galactoside 2-alpha-L-fucosyltransferase 2(GDP-L-fucose:beta-D-galactoside 2-alpha-L-fucosyltransferase 2)(Alpha(1,2)FT 2) (Fucosyltransferase 2) (Secretor blood groupalpha-2-fucosyltransferase) (Secretor factor) (Se) (SE2); (2175:) Galactoside 3(4)-L-fucosyltransferase (Blood group Lewisalpha-4-fucosyltransferase) (Lewis FT) (Fucosyltransferase 3)(FUCT-III); (2176:) galactosyl transferase-associated protein [Homo sapiens]; (2177:) galactosylceramidase (EC 3.2.1.46) precursor - human; (2178:) galactosylceramidase isoform a precursor [Homo sapiens]; (2179:) galactosylceramidase isoform b precursor [Homo sapiens]; (2180:) Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 1(Beta-1,3-glucuronyltransferase 1) (Glucuronosyltransferase-P)(GlcAT-P) (UDP-GlcUA:glycoprotein beta-1,3-glucuronyltransferase)(GlcUAT-P); (2181:) Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 2(Beta-1,3-glucuronyltransferase 2) (Glucuronosyltransferase-S)(GlcAT-S) (UDP-glucuronosyltransferase-S) (GlcAT-D); (2182:) galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 2[Homo sapiens]; (2183:) Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3(Beta-1,3-glucuronyltransferase 3) (Glucuronosyltransferase-I)(GlcAT-I) (UDP-GlcUA:Gal beta-1,3-Gal-R glucuronyltransferase)(GlcUAT-I); (2184:) Galanin receptor type 1

(GAL1-R) (GALR1); (2185:) Galanin receptor type 2 (GAL2-R) (GALR2); (2186:) Galanin receptor type 3 (GAL3-R) (GALR3); (2187:) galctocerebrosidase; (2188:) galectin 3 [Homo sapiens]; (2189:) GalNAc 4-sulfotransferase [Homo sapiens]; (2190:) gamma isoform of regulatory subunit B55, protein phosphatase 2isoform a [Homo sapiens]; (2191:) gamma isoform of regulatory subunit B55, protein phosphatase 2isoform b [Homo sapiens]; (2192:) gamma isoform of regulatory subunit B56, protein phosphatase 2Aisoform a [Homo sapiens]; (2193:) gamma isoform of regulatory subunit B56, protein phosphatase 2Aisoform b [Homo sapiens]; (2194:) gamma isoform of regulatory subunit B56, protein phosphatase 2Aisoform c [Homo sapiens]; (2195:) gamma isoform of regulatory subunit B56, protein phosphatase 2Aisoform d [Homo sapiens]; (2196:) Gamma-aminobutyric acid type B receptor, subunit 1 precursor(GABA-B receptor 1) (GABA-B-R1) (Gb1); (2197:) Gamma-aminobutyric acid type B receptor, subunit 2 precursor(GABA-B receptor 2) (GABA-B-R2) (Gb2) (GABABR2) (G-protein coupledreceptor 51) (HG20); (2198:) gamma-butyrobetaine dioxygenase [Homo sapiens]; (2199:) gamma-catenin [Homo sapiens]; (2200:) gamma-glutamyl carboxylase [Homo sapiens]; (2201:) gamma-glutamyl hydrolase (EC 3.4.19.9) - human; (2202:) Gamma-glutamyl hydrolase precursor (Gamma-Glu-X carboxypeptidase)(Conjugase) (GH); (2203:) gamma-glutamyl hydrolase precursor [Homo sapiens]; (2204:) gamma-glutamyltransferase 1 precursor [Homo sapiens]; (2205:) "Gamma-glutamyltransferase 5 precursor (Gamma-glutamyltranspeptidase5) (Gamma-glutamyltransferase-like activity 1) (GGT-rel) [Contains:Gamma-glutamyltransferase 5 heavy chain; Gamma-glutamyltransferase5 light chain]."; (2206:) gamma-glutamyltransferase-like activity 1 [Homo sapiens]; (2207:) gamma-glutamyltransferase-like activity 4 [Homo sapiens]; (2208:) "Gamma-glutamyltranspeptidase 1 precursor (Gamma-glutamyltransferase1) (GGT 1) (CD224 antigen) [Contains:) Gamma-glutamyltranspeptidase1 heavy chain; Gamma-glutamyltranspeptidase 1 light chain]."; (2209:) gamma-glutmyl transpeptidase-related protein; (2210:) Gamma-secretase subunit APH-1A (APH-1a) (Aph-1alpha)(Presenilin-stabilization factor); (2211:) Gamma-secretase subunit PEN-2 (Presenilin enhancer protein 2); (2212:) ganglioside-specific alpha-2, 8-polysialyltransferase; (2213:) gastric inhibitory polypeptide preproprotein [Homo sapiens]; (2214:) Gastric inhibitory polypeptide receptor precursor (GIP-R)(Glucose-dependent insulinotropic polypeptide receptor); (2215:) gastric lipase precursor [Homo sapiens]; (2216:) Gastric triacylglycerol lipase precursor (Gastric lipase) (GL); (2217:) Gastrin/cholecystokinin type B receptor (CCK-B receptor) (CCK-

BR)(Cholecystokinin-2 receptor) (CCK2-R); (2218:) gastrin-releasing peptide isoform 1 preproprotein [Homo sapiens]; (2219:) gastrin-releasing peptide isoform 2 preproprotein [Homo sapiens]; (2220:) gastrin-releasing peptide isoform 3 preproprotein [Homo sapiens]; (2221:) Gastrin-releasing peptide receptor (GRP-R) (GRP-preferring bombesinreceptor); (2222:) GCNT2 [Homo sapiens]; (2223:) GCNT3 protein [Homo sapiens]; (2224:) GDNF family receptor alpha-1 precursor (GFR-alpha-1) (GDNF receptoralpha) (GDNFR-alpha) (TGF-beta-related neurotrophic factor receptor1) (RET ligand 1); (2225:) GDNF family receptor alpha-2 precursor (GFR-alpha-2) (Neurturinreceptor alpha) (NTNR-alpha) (NRTNR-alpha) (TGF-beta-relatedneurotrophic factor receptor 2) (GDNF receptor beta) (GDNFR-beta)(RET ligand 2); (2226:) GDNF family receptor alpha-3 precursor (GFR-alpha-3); (2227:) GDNF family receptor alpha-4 precursor (GFR-alpha-4) (Persephinreceptor); (2228:) GDNF family receptor alpha-like precursor; (2229:) GDP-D-mannose-4,6-dehydratase [Homo sapiens]; (2230:) GDP-L-fucose pyrophosphorylase [Homo sapiens]; (2231:) GDP-mannose 4,6-dehydratase [Homo sapiens]; (2232:) GDP-mannose pyrophosphorylase A [Homo sapiens]; (2233:) GDP-mannose pyrophosphorylase B isoform 1 [Homo sapiens]; (2234:) GDP-mannose pyrophosphorylase B isoform 2 [Homo sapiens]; (2235:) gelatinase, type IV collagenase {N-terminal} [human, neutrophils,Peptide Partial, 19 aa]; (2236:) Gephyrin [Homo sapiens]; (2237:) gephyrin isoform 1 [Homo sapiens]; (2238:) gephyrin isoform 2 [Homo sapiens]; (2239:) geranylgeranyl diphosphate synthase 1 isoform A [Homo sapiens]; (2240:) geranylgeranyl diphosphate synthase 1 isoform B [Homo sapiens]; (2241:) geranylgeranyl transferase II [Homo sapiens]; (2242:) Geranylgeranyl transferase type-2 alpha subunit (Geranylgeranyltransferase type II alpha subunit) (Rab geranylgeranyltransferasealpha subunit) (Rab geranyl-geranyltransferase alpha subunit) (RabGG transferase alpha) (Rab GGTase alpha); (2243:) Geranylgeranyl transferase type-2 subunit beta (Geranylgeranyltransferase type II subunit beta) (Rab geranylgeranyltransferasesubunit beta) (Rab geranyl-geranyltransferase subunit beta) (Rab GGtransferase beta) (Rab GGTase beta); (2244:) ghrelin precursor [Homo sapiens]; (2245:) GlcNac-1-P transferase [Homo sapiens]; (2246:) GlcNAc-phosphotransferase precursor [Homo sapiens]; (2247:) Globoside alpha-1,3-N-acetylgalactosaminyltransferase 1 (Forssmanglycolipid synthetase-like protein); (2248:) glomulin [Homo sapiens]; (2249:) Glucagon receptor precursor (GL-R); (2250:) Glucagon-like peptide 1 receptor precursor (GLP-1 receptor)(GLP-1-R) (GLP-1R); (2251:) Glucagon-like peptide 2 receptor precursor (GLP-2 receptor)(GLP-2-R) (GLP-2R); (2252:) glucan (1,4-alpha-),

branching enzyme 1 (glycogen branching enzyme)[Homo sapiens]; (2253:) Glucan , branching enzyme 1 variant [Homo sapiens]; (2254:) glucocerebrosidase precursor [Homo sapiens]; (2255:) Glucocorticoid receptor (GR); (2256:) Glucokinase (Hexokinase-4) (Hexokinase type IV) (HK IV) (HK4)(Hexokinase-D); (2257:) glucokinase isoform 1 [Homo sapiens]; (2258:) glucokinase isoform 2 [Homo sapiens]; (2259:) glucokinase isoform 3 [Homo sapiens]; (2260:) Glucokinase regulatory protein (Glucokinase regulator); (2261:) glucokinase regulatory protein [Homo sapiens]; (2262:) glucosamine (N-acetyl)-6-sulfatase precursor [Homo sapiens]; (2263:) glucosamine-fructose-6-phosphate aminotransferase [Homo sapiens]; (2264:) Glucosaminyl (N-acetyl) transferase 1, core 2(beta-1,6-N-acetylglucosaminyltransferase) [Homo sapiens]; (2265:) Glucosaminyl (N-acetyl) transferase 2, I-branching enzyme (I bloodgroup) [Homo sapiens]; (2266:) glucosaminyl (N-acetyl) transferase 2, I-branching enzyme isoform A[Homo sapiens]; (2267:) glucosaminyl (N-acetyl) transferase 2, I-branching enzyme isoform B[Homo sapiens]; (2268:) glucosaminyl (N-acetyl) transferase 2, I-branching enzyme isoform C[Homo sapiens]; (2269:) Glucosaminyl (N-acetyl) transferase 2, I-branching enzyme, isoformB [Homo sapiens]; (2270:) glucosaminyl (N-acetyl) transferase 3, mucin type [Homo sapiens]; (2271:) glucose phosphate isomerase [Homo sapiens]; (2272:) glucose transporter 4 [Homo sapiens]; (2273:) Glucose-6-phosphatase (G6Pase) (G-6-Pase); (2274:) glucose-6-phosphatase, catalytic subunit [Homo sapiens]; (2275:) Glucose-6-phosphate 1-dehydrogenase (G6PD); (2276:) glucose-6-phosphate dehydrogenase isoform a [Homo sapiens]; (2277:) glucose-6-phosphate dehydrogenase isoform b [Homo sapiens]; (2278:) "glucosidase, alpha; neutral C [Homo sapiens]."; (2279:) glucuronidase, beta [Homo sapiens]; (2280:) glucuronyltransferase [Homo sapiens]; (2281:) glucuronyltransferase I [Homo sapiens]; (2282:) Glutamate [NMDA] receptor subunit 3A precursor(N-methyl-D-aspartate receptor subtype NR3A) (NMDAR-L); (2283:) Glutamate [NMDA] receptor subunit 3B precursor(N-methyl-D-aspartate receptor subtype NR3B) (NR3B) (NMDAR3B); (2284:) Glutamate [NMDA] receptor subunit epsilon 1 precursor (N-methylD-aspartate receptor subtype 2A) (NR2A) (NMDAR2A) (hNR2A); (2285:) Glutamate [NMDA] receptor subunit epsilon 2 precursor (N-methylD-aspartate receptor subtype 2B) (NR2B) (NMDAR2B)(N-methyl-D-aspartate receptor subunit 3) (NR3) (hNR3); (2286:) Glutamate [NMDA] receptor subunit epsilon 3 precursor (N-methylD-aspartate receptor subtype 2C) (NR2C) (NMDAR2C); (2287:) Glutamate [NMDA] receptor subunit epsilon 4 precursor (N-methylD-aspartate receptor subtype 2D) (NR2D) (NMDAR2D) (EB11); (2288:)

Glutamate [NMDA] receptor subunit zeta 1 precursor(N-methyl-D-aspartate receptor subunit NR1); (2289:) Glutamate carboxypeptidase 2 (Glutamate carboxypeptidase II)(Membrane glutamate carboxypeptidase) (mGCP)(N-acetylated-alpha-linked acidic dipeptidase I) (NAALADase I)(Pteroylpoly-gamma-glutamate carboxypeptidase)(Folylpoly-gamma-glutamate carboxypeptidase) (FGCP) (Folatehydrolase 1) (Prostate-specific membrane antigen) (PSMA) (PSM); (2290:) Glutamate decarboxylase 1 (Glutamate decarboxylase 67 kDa isoform)(GAD-67) (67 kDa glutamic acid decarboxylase); (2291:) glutamate decarboxylase 1 isoform GAD25 [Homo sapiens]; (2292:) glutamate decarboxylase 1 isoform GAD67 [Homo sapiens]; (2293:) glutamate decarboxylase 2 [Homo sapiens]; (2294:) glutamate dehydrogenase 1 [Homo sapiens]; (2295:) Glutamate dehydrogenase 1, mitochondrial precursor (GDH); (2296:) glutamate dehydrogenase 2 [Homo sapiens]; (2297:) Glutamate receptor 1 precursor (GluR-1) (GluR-A) (GluR-K1)(Glutamate receptor ionotropic, AMPA 1) (AMPA-selective glutamatereceptor 1); (2298:) Glutamate receptor 2 precursor (GluR-2) (GluR-B) (GluR-K2)(Glutamate receptor ionotropic, AMPA 2) (AMPA-selective glutamatereceptor 2); (2299:) Glutamate receptor 3 precursor (GluR-3) (GluR-C) (GluR-K3)(Glutamate receptor ionotropic, AMPA 3) (AMPA-selective glutamatereceptor 3); (2300:) Glutamate receptor 4 precursor (GluR-4) (GluR4) (GluR-D) (Glutamatereceptor ionotropic, AMPA 4) (AMPA-selective glutamate receptor 4); (2301:) Glutamate receptor delta-1 subunit precursor (GluR delta-1); (2302:) Glutamate receptor delta-2 subunit precursor (GluR delta-2); (2303:) Glutamate receptor, ionotropic kainate 1 precursor (Glutamatereceptor 5) (GluR-5) (GluR5) (Excitatory amino acid receptor 3)(EAA3); (2304:) Glutamate receptor, ionotropic kainate 2 precursor (Glutamatereceptor 6) (GluR-6) (GluR6) (Excitatory amino acid receptor 4)(EAA4); (2305:) Glutamate receptor, ionotropic kainate 3 precursor (Glutamatereceptor 7) (GluR-7) (GluR7) (Excitatory amino acid receptor 5)(EAA5); (2306:) Glutamate receptor, ionotropic kainate 4 precursor (Glutamatereceptor KA-1) (KA1) (Excitatory amino acid receptor 1) (EAA1); (2307:) Glutamate receptor, ionotropic kainate 5 precursor (Glutamatereceptor KA-2) (KA2) (Excitatory amino acid receptor 2) (EAA2); (2308:) glutamate-5-semialdehyde dehydrogenase (EC 1.2.1.41) - human(fragments); (2309:) Glutamate--cysteine ligase catalytic subunit(Gamma-glutamylcysteine synthetase) (Gamma-ECS) (GCS heavy chain); (2310:) glutamate-cysteine ligase regulatory protein [Homo sapiens]; (2311:) glutamate-cysteine ligase, catalytic subunit [Homo sapiens]; (2312:) glutamic gamma-semialdehyde dehydrogenase; (2313:) glutaminase 2 [Homo sapiens]; (2314:) glutaminase C [Homo sapiens];

(2315:) glutamine synthetase [Homo sapiens]; (2316:) glutaminyl-peptide cyclotransferase precursor [Homo sapiens]; (2317:) Glutaminyl-tRNA synthetase (Glutamine--tRNA ligase) (GlnRS); (2318:) glutaminyl-tRNA synthetase [Homo sapiens]; (2319:) Glutaredoxin-2, mitochondrial precursor; (2320:) glutaryl-CoA dehydrogenase [Homo sapiens]; (2321:) Glutaryl-CoA dehydrogenase, mitochondrial precursor (GCD); (2322:) glutaryl-Coenzyme A dehydrogenase isoform a precursor [Homosapiens]; (2323:) glutaryl-Coenzyme A dehydrogenase isoform b precursor [Homosapiens]; (2324:) glutathione peroxidase [Homo sapiens]; (2325:) glutathione peroxidase 1 isoform 1 [Homo sapiens]; (2326:) glutathione peroxidase 1 isoform 2 [Homo sapiens]; (2327:) glutathione peroxidase 4 isoform A precursor [Homo sapiens]; (2328:) glutathione peroxidase 4 isoform B precursor [Homo sapiens]; (2329:) glutathione peroxidase 4 isoform C precursor [Homo sapiens]; (2330:) Glutathione Reductase (E.C.1.6.4.2) (Oxidized) Complex WithGlutathione Disulfide And Nadp+; (2331:) Glutathione Reductase (E.C.1.6.4.2) Carboxymethylated At Cys 58Complex With Phosphate; (2332:) Glutathione Reductase (E.C.1.6.4.2) Complex With Covalently BoundGlutathione And Phosphate; (2333:) Glutathione Reductase (E.C.1.6.4.2) Modified By Bcnu(1,3-Bis(2-Chloroethyl)-1-Nitrosourea) At Cys 58 Complexed WithPhosphate; (2334:) Glutathione Reductase (E.C.1.6.4.2) Modified By Hecnu(1-(2-Chloroethyl)-3-(2-Hydroxyethyl)-1-Nitrosourea) At Cys 58Complexed With Phosphate; (2335:) glutathione reductase [Homo sapiens]; (2336:) Glutathione reductase, mitochondrial precursor (GR) (GRase); (2337:) glutathione S-transferase A1 [Homo sapiens]; (2338:) glutathione S-transferase A3 [Homo sapiens]; (2339:) Glutathione S-transferase A4 (Glutathione S-transferase A4-4) (GSTclass-alpha member 4); (2340:) glutathione S-transferase A4 [Homo sapiens]; (2341:) glutathione S-transferase M1 isoform 1 [Homo sapiens]; (2342:) glutathione S-transferase M1 isoform 2 [Homo sapiens]; (2343:) glutathione S-transferase M3 [Homo sapiens]; (2344:) Glutathione S-transferase Mu 1 (GSTM1-1) (GST class-mu 1)(GSTM1a-1a) (GSTM1b-1b) (HB subunit 4) (GTH4); (2345:) glutathione S-transferase theta 1 [Homo sapiens]; (2346:) Glutathione S-transferase theta-1 (GST class-theta-1) (Glutathionetransferase T1-1); (2347:) glutathione transferase [Homo sapiens]; (2348:) glutathione transferase A4-4 [Homo sapiens]; (2349:) glutathione transferase kappa 1 [Homo sapiens]; (2350:) glutathione transferase T1-1 [Homo sapiens]; (2351:) glutathione transferase zeta 1 isoform 1 [Homo sapiens]; (2352:) glutathione transferase zeta 1 isoform 2 [Homo sapiens]; (2353:) glutathione transferase zeta 1 isoform 3 [Homo sapiens]; (2354:) glutathione transferase;

(2355:) glyceraldehyde-3-phosphate dehydrogenase [Homo sapiens]; (2356:) Glycerol kinase (ATP:glycerol 3-phosphotransferase) (Glycerokinase)(GK); (2357:) Glycerol kinase, testis specific 1 (ATP:glycerol3-phosphotransferase) (Glycerokinase) (GK); (2358:) Glycerol kinase, testis specific 2 (ATP:glycerol3-phosphotransferase) (Glycerokinase) (GK); (2359:) glycerol-3-phosphate dehydrogenase 2 (mitochondrial) [Homosapiens]; (2360:) Glycerol-3-phosphate dehydrogenase, mitochondrial precursor (GPD-M)(GPDH-M) (mtGPD); (2361:) glycine amidinotransferase (L-arginine:glycine amidinotransferase)[Homo sapiens]; (2362:) Glycine amidinotransferase, mitochondrial precursor(L-arginine:glycine amidinotransferase) (Transamidinase) (AT); (2363:) Glycine C-acetyltransferase (2-amino-3-ketobutyrate coenzyme Aligase) [Homo sapiens]; (2364:) glycine C-acetyltransferase precursor [Homo sapiens]; (2365:) Glycine cleavage system H protein, mitochondrial precursor; (2366:) glycine cleavage system protein H (aminomethyl carrier) [Homosapiens]; (2367:) glycine dehydrogenase (decarboxylating) [Homo sapiens]; (2368:) glycine N-methyltransferase [Homo sapiens]; (2369:) Glycine receptor subunit alpha-1 precursor (Glycine receptor 48 kDasubunit) (Glycine receptor strychnine-binding subunit); (2370:) Glycine receptor subunit alpha-2 precursor; (2371:) Glycine receptor subunit alpha-3 precursor; (2372:) Glycine receptor subunit beta precursor (Glycine receptor 58 kDasubunit); (2373:) glycine-N-acyltransferase isoform a [Homo sapiens]; (2374:) glycine-N-acyltransferase isoform b [Homo sapiens]; (2375:) glycoasparaginase; (2376:) Glycogen [starch] synthase, liver; (2377:) Glycogen [starch] synthase, muscle; (2378:) "Glycogen debranching enzyme (Glycogen debrancher) [Includes:4-alpha-glucanotransferase (Oligo-1,4-1,4-glucantransferase);Amylo-alpha-1,6-glucosidase (Amylo-1,6-glucosidase) (Dextrin6-alpha-D-glucosidase)]."; (2379:) glycogen debranching enzyme [Homo sapiens]; (2380:) glycogen debranching enzyme isoform 1 [Homo sapiens]; (2381:) glycogen debranching enzyme isoform 2 [Homo sapiens]; (2382:) glycogen debranching enzyme isoform 3 [Homo sapiens]; (2383:) glycogen debranching enzyme isoform 4 [Homo sapiens]; (2384:) glycogen debranching enzyme isoform 6 [Homo sapiens]; (2385:) glycogen phosphorylase [Homo sapiens]; (2386:) Glycogen phosphorylase, brain form; (2387:) Glycogen phosphorylase, liver form; (2388:) Glycogen phosphorylase, muscle form (Myophosphorylase); (2389:) glycogen synthase kinase 3 beta [Homo sapiens]; (2390:) Glycogen synthase kinase-3 beta (GSK-3 beta); (2391:) glycogen-debranching enzyme [Homo sapiens]; (2392:) glycophorin A precursor [Homo sapiens]; (2393:) glycoprotein V (platelet) [Homo sapiens]; (2394:) glycoprotein-

fucosylgalactosidealpha-N-acetylgalactosaminyltransferase (EC 2.4.1.40) A1 allele[validated] - human; (2395:) glycosylphosphatidylinositol specific phospholipase D1 isoform 1precursor [Homo sapiens]; (2396:) glycosylphosphatidylinositol specific phospholipase D1 isoform 2precursor [Homo sapiens]; (2397:) Glycylpeptide N-tetradecanoyltransferase 1 (PeptideN-myristoyltransferase 1) (Myristoyl-CoA:proteinN-myristoyltransferase 1) (NMT 1) (Type I N-myristoyltransferase); (2398:) glycyl-tRNA synthetase [Homo sapiens]; (2399:) glyoxalase I [Homo sapiens]; (2400:) glyoxylate reductase/hydroxypyruvate reductase [Homo sapiens]; (2401:) Glyoxylate reductase/hydroxypyruvate reductase; (2402:) GM2 ganglioside activator precursor [Homo sapiens]; (2403:) Golgi autoantigen, golgin subfamily a, 2 [Homo sapiens]; (2404:) golgi autoantigen, golgin subfamily b, macrogolgin (withtransmembrane signal), 1 [Homo sapiens]; (2405:) Golgi reassembly stacking protein 1 [Homo sapiens]; (2406:) Golgi-specific brefeldin A-resistance guanine nucleotide exchangefactor 1 (BFA-resistant GEF 1); (2407:) Golli-mbp isoform 1 [Homo sapiens]; (2408:) Golli-mbp isoform 2 [Homo sapiens]; (2409:) Gonadotropin-releasing hormone II receptor (Type II GnRH receptor)(GnRH-II-R); (2410:) Gonadotropin-releasing hormone receptor (GnRH receptor) (GnRH-R); (2411:) gp180-carboxypeptidase D-like enzyme [Homo sapiens]; (2412:) GPI mannosyltransferase 1 (GPI mannosyltransferase I) (GPI-MT-I)(Phosphatidylinositol-glycan biosynthesis class M protein) (PIG-M); (2413:) GPI mannosyltransferase 2 (GPI mannosyltransferase II) (GPI-MT-II)(Phosphatidylinositol-glycan biosynthesis class V protein) (PIG-V); (2414:) GPI transamidase component PIG-T precursor(Phosphatidylinositol-glycan biosynthesis class T protein); (2415:) GPI-anchor transamidase precursor (GPI transamidase)(Phosphatidylinositol-glycan biosynthesis class K protein) (PIG-K)(hGPI8); (2416:) G-protein coupled bile acid receptor 1 (Membrane-type receptor forbile acids) (M-BAR) (hGPCR19) (BG37) (hBG37); (2417:) G-protein coupled receptor 120 (G-protein coupled receptor PGR4)(G-protein coupled receptor GT01) (G-protein coupled receptor 129); (2418:) G-protein coupled receptor 143 (Ocular albinism type 1 protein); (2419:) G-protein coupled receptor 15 (BOB); (2420:) G-protein coupled receptor 56 precursor (TM7XN1 protein); (2421:) G-protein coupled receptor 64 precursor (Epididymis-specificprotein 6) (He6 receptor); (2422:) G-protein coupled receptor 98 precursor (Monogenic audiogenicseizure susceptibility protein 1 homolog) (Very large G-proteincoupled receptor 1) (Usher syndrome type-2C protein); (2423:) G-protein coupled receptor family C group 5 member B precursor(Retinoic acid-induced gene 2 protein) (RAIG-2) (A-69G12.1); (2424:) G-

protein coupled receptor family C group 5 member C precursor(Retinoic acid-induced gene 3 protein) (RAIG-3); (2425:) G-protein coupled receptor family C group 5 member D; (2426:) G-protein coupled receptor family C group 6 member A precursor(hGPRC6A) (G-protein coupled receptor 33) (hGPCR33); (2427:) Grainyhead-like protein 1 homolog (Transcription factor CP2-like 2)(Transcription factor LBP-32) (NH32) (Mammalian grainyhead); (2428:) Granulocyte colony-stimulating factor receptor precursor (G-CSF-R)(CD114 antigen); (2429:) Granulocyte-macrophage colony-stimulating factor receptor alphachain precursor (GM-CSF-R-alpha) (GMR) (CD116 antigen) (CDw116); (2430:) Granzyme A precursor (Cytotoxic T-lymphocyte proteinase 1)(Hanukkah factor) (H factor) (HF) (Granzyme-1) (CTL tryptase); (2431:) Granzyme B precursor (T-cell serine protease 1-3E) (CytotoxicT-lymphocyte proteinase 2) (Lymphocyte protease) (SECT)(Granzyme-2) (Cathepsin G-like 1) (CTSGL1) (CTLA-1) (Humanlymphocyte protein) (HLP) (C11); (2432:) granzyme B precursor [Homo sapiens]; (2433:) Granzyme H precursor (Cytotoxic T-lymphocyte proteinase) (CathepsinG-like 2) (CTSGL2) (CCP-X) (Cytotoxic serine protease C) (CSP-C); (2434:) granzyme M precursor [Homo sapiens]; (2435:) Green-sensitive opsin (Green cone photoreceptor pigment); (2436:) Group 3 secretory phospholipase A2 precursor (Group III secretoryphospholipase A2) (Phosphatidylcholine 2-acylhydrolase GIII) (GIIIsPLA2); (2437:) group III secreted phospholipase A2 [Homo sapiens]; (2438:) growth factor receptor-bound protein 2 isoform 1 [Homo sapiens]; (2439:) growth factor receptor-bound protein 2 isoform 2 [Homo sapiens]; (2440:) growth hormone 1 isoform 1 [Homo sapiens]; (2441:) growth hormone 1 isoform 2 [Homo sapiens]; (2442:) growth hormone 1 isoform 3 [Homo sapiens]; (2443:) growth hormone 1 isoform 4 [Homo sapiens]; (2444:) growth hormone 1 isoform 5 [Homo sapiens]; (2445:) Growth hormone receptor precursor (GH receptor) (Somatotropinreceptor) [Contains:) Growth hormone-binding protein (GH-bindingprotein) (GHBP) (Serum-binding protein)]; (2446:) Growth hormone secretagogue receptor type 1 (GHS-R) (GH-releasingpeptide receptor) (GHRP) (Ghrelin receptor); (2447:) Growth hormone-releasing hormone receptor precursor (GHRH receptor)(GRF receptor) (GRFR); (2448:) growth-inhibiting protein 17 [Homo sapiens]; (2449:) G-T3 synthase; (2450:) GTP cyclohydrase I [Homo sapiens]; (2451:) GTP cyclohydrolase 1 isoform 1 [Homo sapiens]; (2452:) GTP cyclohydrolase 1 isoform 2 [Homo sapiens]; (2453:) GTP cyclohydrolase 1 isoform 3 [Homo sapiens]; (2454:) GTP cyclohydrolase I (GTP-CH-I); (2455:) GTP cyclohydrolase I [Homo sapiens]; (2456:) GTPase activating Rap/RanGAP domain-like 1 isoform 1 [Homosapiens]; (2457:)

GTPase activating Rap/RanGAP domain-like 1 isoform 2 [Homosapiens]; (2458:) GTPase ERas precursor (E-Ras) (Embryonic stem cell-expressed Ras); (2459:) GTPase HRas precursor (Transforming protein p21) (p21ras) (H-Ras-1)(c-H-ras); (2460:) GTPase KRas (K-Ras 2) (Ki-Ras) (c-K-ras) (c-Ki-ras); (2461:) GTPase NRas precursor (Transforming protein N-Ras); (2462:) GTP-binding protein Rit1 (Ras-like protein expressed in manytissues) (Ras-like without CAAX protein 1); (2463:) guanine deaminase [Homo sapiens]; (2464:) guanine nucleotide exchange factor p532 [Homo sapiens]; (2465:) guanosine monophosphate reductase [Homo sapiens]; (2466:) guanylate cyclase 1, soluble, alpha 2 [Homo sapiens]; (2467:) guanylate cyclase activator 1A (retina) [Homo sapiens]; (2468:) "Guanylate cyclase activator 2B precursor [Contains:) Guanylatecyclase C-activating peptide 2 (Guanylate cyclase C-activatingpeptide II) (GCAP-II); Uroguanylin (UGN)]."; (2469:) Guanylate cyclase soluble subunit alpha-2 (GCS-alpha-2); (2470:) Guanylate cyclase soluble subunit alpha-3 (GCS-alpha-3) (Solubleguanylate cyclase large subunit) (GCS-alpha-1); (2471:) Guanylate cyclase soluble subunit beta-1 (GCS-beta-1) (Solubleguanylate cyclase small subunit) (GCS-beta-3); (2472:) Guanylate cyclase soluble subunit beta-2 (GCS-beta-2); (2473:) guanylate cyclase:SUBUNIT=alpha2; (2474:) "Guanylin precursor (Guanylate cyclase activator 2A) (Guanylatecyclase-activating protein 1) (Gap-I) [Contains:) HMW-guanylin;Guanylin]."; (2475:) H(+)-transporting two-sector ATPase [Homo sapiens]; (2476:) H+-exporting ATPase (EC 3.6.3.6) chain D, vacuolar - human; (2477:) H2A histone family, member O [Homo sapiens]; (2478:) HACL1 protein [Homo sapiens]; (2479:) head and neck tumor and metastasis related protein [Homo sapiens]; (2480:) heat shock 27kDa protein 1 [Homo sapiens]; (2481:) heat shock 27kDa protein 2 [Homo sapiens]; (2482:) heat shock 70kDa protein 5 [Homo sapiens]; (2483:) heat shock-like protein 1 [Homo sapiens]; (2484:) HEAT-like (PBS lyase) repeat containing 1 [Homo sapiens]; (2485:) Heat-stable enterotoxin receptor precursor (GC-C) (Intestinalguanylate cyclase) (STA receptor) (hSTAR); (2486:) hect domain and RLD 5 [Homo sapiens]; (2487:) hedgehog acyltransferase [Homo sapiens]; (2488:) heme oxygenase (decyclizing) 1 [Homo sapiens]; (2489:) heme oxygenase (decyclizing) 2 [Homo sapiens]; (2490:) heparan sulfate (glucosamine) 3-O-sulfotransferase 5 [Homosapiens]; (2491:) heparan sulfate (glucosamine) 3-O-sulfotransferase 6 [Homosapiens]; (2492:) heparan sulfate 2-O-sulfotransferase 1 [Homo sapiens]; (2493:) heparan sulfate 3-O-sulfotransferase-1 precursor [Homo sapiens]; (2494:) heparan sulfate 6-O-sulfotransferase [Homo sapiens]; (2495:) heparan sulfate 6-O-sulfotransferase 3 [Homo sapiens]; (2496:) heparan sulfate D-

glucosaminyl 3-O-sulfotransferase 2 [Homosapiens]; (2497:) heparan sulfate D-glucosaminyl 3-O-sulfotransferase 1 precursor[Homo sapiens]; (2498:) heparan sulfate D-glucosaminyl 3-O-sulfotransferase 3A1 [Homosapiens]; (2499:) heparan sulfate D-glucosaminyl 3-O-sulfotransferase 3B1 [Homosapiens]; (2500:) heparan sulfate D-glucosaminyl 3-O-sulfotransferase 4 [Homosapiens]; (2501:) Heparan sulfate glucosamine 3-O-sulfotransferase 1 precursor(Heparan sulfate D-glucosaminyl 3-O-sulfotransferase 1) (Heparansulfate 3-O-sulfotransferase 1) (h3-OST-1); (2502:) Heparan sulfate glucosamine 3-O-sulfotransferase 3A1 (Heparansulfate D-glucosaminyl 3-O-sulfotransferase 3A1) (Heparan sulfate3-O-sulfotransferase 3A1) (h3-OST-3A); (2503:) Heparan sulfate glucosamine 3-O-sulfotransferase 3B1 (Heparansulfate D-glucosaminyl 3-O-sulfotransferase 3B1) (Heparan sulfate3-O-sulfotransferase 3B1) (h3-OST-3B); (2504:) Heparan sulfate glucosamine 3-O-sulfotransferase 5 (Heparan sulfateD-glucosaminyl 3-O-sulfotransferase 5) (Heparan sulfate3-O-sulfotransferase 5) (h3-OST-5); (2505:) Heparan sulfate glucosamine 3-O-sulfotransferase 6 (Heparan sulfateD-glucosaminyl 3-O-sulfotransferase 6) (Heparan sulfate3-O-sulfotransferase 6) (h3-OST-6); (2506:) heparanase [Homo sapiens]; (2507:) "Heparanase precursor (Heparanase-1) (Hpa1) (Endo-glucoronidase)[Contains:) Heparanase 8 kDa subunit; Heparanase 50 kDa subunit]."; (2508:) heparanase precursor [Homo sapiens]; (2509:) Heparanase-2 (Hpa2); (2510:) Heparan-sulfate 6-O-sulfotransferase 1 (HS6ST-1); (2511:) Heparan-sulfate 6-O-sulfotransferase 2 (HS6ST-2); (2512:) Heparan-sulfate 6-O-sulfotransferase 3 (HS6ST-3); (2513:) Heparin-binding EGF-like growth factor precursor (HB-EGF) (HBEGF)(Diphtheria toxin receptor) (DT-R); (2514:) Hepatic triacylglycerol lipase precursor (Hepatic lipase) (HL); (2515:) Hepatitis A virus cellular receptor 1 precursor (HAVcr-1) (T cellimmunoglobulin and mucin domain-containing protein 1) (TIMD-1) (Tcell membrane protein 1) (TIM-1) (TIM); (2516:) Hepatocyte growth factor receptor precursor (HGF receptor) (Scatterfactor receptor) (SF receptor) (HGF/SF receptor) (Metproto-oncogene tyrosine kinase) (c-Met); (2517:) Hepatocyte nuclear factor 4-alpha (HNF-4-alpha) (Transcriptionfactor HNF-4) (Transcription factor 14); (2518:) Hepatocyte nuclear factor 4-gamma (HNF-4-gamma); (2519:) herpesvirus associated ubiquitin-specific protease (HAUSP) [Homosapiens]; (2520:) "HERV-K_3q27.3 provirus ancestral Pol protein [Includes:) Reversetranscriptase (RT) ; Ribonuclease H (RNase H); Integrase (IN)]."; (2521:) HERV-K_5q33.3 provirus ancestral Pro protein (HERV-K10 Pro protein)(HERV-K107 Pro protein) (Protease) (Proteinase) (PR); (2522:) "HERV-K_7p22.1 provirus ancestral Pol protein (HERV-

K(HML-2.HOM) Polprotein) (HERV-K108 Pol protein) (HERV-K(C7) Pol protein)[Includes:) Reverse transcriptase (RT) ; Ribonuclease H (RNase H);Integrase (IN)]."; (2523:) heterogeneous nuclear ribonucleoprotein AB isoform a [Homosapiens]; (2524:) heterogeneous nuclear ribonucleoprotein AB isoform b [Homosapiens]; (2525:) hexokinase 1 [Homo sapiens]; (2526:) hexokinase 1 isoform HKI [Homo sapiens]; (2527:) hexokinase 1 isoform HKI-R [Homo sapiens]; (2528:) hexokinase 1 isoform HKI-ta/tb [Homo sapiens]; (2529:) hexokinase 1 isoform HKI-td [Homo sapiens]; (2530:) hexokinase 2 [Homo sapiens]; (2531:) hexokinase 3 [Homo sapiens]; (2532:) Hexokinase-1 (Hexokinase type I) (HK I) (Brain form hexokinase); (2533:) Hexokinase-2 (Hexokinase type II) (HK II) (Muscle form hexokinase); (2534:) Hexokinase-3 (Hexokinase type III) (HK III); (2535:) hexosaminidase A preproprotein [Homo sapiens]; (2536:) hexosaminidase B preproprotein [Homo sapiens]; (2537:) hexose-6-phosphate dehydrogenase precursor [Homo sapiens]; (2538:) HGD protein [Homo sapiens]; (2539:) "HHR6A (Human homologue of yeast RAD 6); putative."; (2540:) "HHR6B (Human homologue of yeast RAD 6); putative."; (2541:) High affinity immunoglobulin epsilon receptor alpha-subunitprecursor (FcERI) (IgE Fc receptor, alpha-subunit) (Fc-epsilonRI-alpha); (2542:) High affinity immunoglobulin epsilon receptor gamma-subunitprecursor (FceRI gamma) (IgE Fc receptor gamma-subunit) (Fc-epsilonRI-gamma); (2543:) High affinity immunoglobulin epsilon receptor subunit beta (FcERI)(IgE Fc receptor, subunit beta) (Fc epsilon receptor I beta-chain); (2544:) High affinity immunoglobulin gamma Fc receptor I precursor(Fc-gamma RI) (FcRI) (IgG Fc receptor I) (CD64 antigen); (2545:) High affinity interleukin-8 receptor A (IL-8R A) (IL-8 receptortype 1) (CXCR-1) (CD181 antigen) (CDw128a); (2546:) High affinity interleukin-8 receptor B (IL-8R B) (CXCR-2) (GRO/MGSAreceptor) (IL-8 receptor type 2) (CD182 antigen) (CDw128b); (2547:) High affinity nerve growth factor receptor precursor (Neurotrophictyrosine kinase receptor type 1) (TRK1 transforming tyrosine kinaseprotein) (p140-TrkA) (Trk-A); (2548:) High-affinity cAMP-specific 3',5'-cyclic phosphodiesterase 7A(HCP1) (TM22); (2549:) High-affinity cAMP-specific and IBMX-insensitive 3',5'-cyclicphosphodiesterase 8A; (2550:) High-affinity cAMP-specific and IBMX-insensitive 3',5'-cyclicphosphodiesterase 8B (HSPDE8B); (2551:) High-affinity cationic amino acid transporter 1 (CAT-1) (CAT1)(System Y+ basic amino acid transporter) (Ecotropic retroviralleukemia receptor homolog) (ERR) (Ecotropic retrovirus receptorhomolog); (2552:) High-affinity cGMP-specific 3',5'-cyclic phosphodiesterase 9A; (2553:) Histamine H1 receptor; (2554:) Histamine H2 receptor (H2R) (Gastric receptor I);

(2555:) Histamine H3 receptor (HH3R) (G-protein coupled receptor 97); (2556:) Histamine H4 receptor (HH4R) (GPRv53) (G-protein coupled receptor105) (GPCR105) (SP9144) (AXOR35); (2557:) Histamine N-methyltransferase (HMT); (2558:) histamine N-methyltransferase [Homo sapiens]; (2559:) histamine N-methyltransferase isoform 1 [Homo sapiens]; (2560:) histamine N-methyltransferase isoform 2 [Homo sapiens]; (2561:) histamine N-methyltransferase isoform 3 [Homo sapiens]; (2562:) histamine N-methyltransferase variant 1 [Homo sapiens]; (2563:) histamine N-methyltransferase variant 2 [Homo sapiens]; (2564:) histamine N-methyltransferase variant 3 [Homo sapiens]; (2565:) histamine N-methyltransferase; (2566:) Histidine acid phosphatase domain containing 1 [Homo sapiens]; (2567:) Histidine acid phosphatase domain containing 2A isoform 4 [Homosapiens]; (2568:) histidine ammonia-lyase [Homo sapiens]; (2569:) histidine decarboxylase [Homo sapiens]; (2570:) histidine triad nucleotide binding protein 1 [Homo sapiens]; (2571:) histidine triad protein member 5 [Homo sapiens]; (2572:) histidyl-tRNA synthetase [Homo sapiens]; (2573:) histidyl-tRNA synthetase-like [Homo sapiens]; (2574:) Histone acetyltransferase HTATIP (60 kDa Tat interactive protein)(Tip60) (HIV-1 Tat interactive protein) (cPLA(2)-interactingprotein); (2575:) Histone acetyltransferase MYST3 (MYST protein 3) (MOZ, YBF2/SAS3,SAS2 and TIP60 protein 3) (Runt-related transcriptionfactor-binding protein 2) (Monocytic leukemia zinc finger protein)(Zinc finger protein 220); (2576:) Histone acetyltransferase MYST4 (MYST protein 4) (MOZ, YBF2/SAS3,SAS2 and TIP60 protein 4) (Histone acetyltransferase MOZ2)(Monocytic leukemia zinc finger protein-related factor) (Histoneacetyltransferase MORF); (2577:) Histone acetyltransferase PCAF (P300/CBP-associated factor) (P/CAF)(Histone acetylase PCAF); (2578:) histone deacetylase 2 [Homo sapiens]; (2579:) histone stem-loop binding protein [Homo sapiens]; (2580:) Histone-lysine N-methyltransferase, H3 lysine-79 specific (HistoneH3-K79 methyltransferase) (H3-K79-HMTase) (DOT1-like protein); (2581:) Histone-lysine N-methyltransferase, H3 lysine-9 specific 1 (HistoneH3-K9 methyltransferase 1) (H3-K9-HMTase 1) (Suppressor ofvariegation 3-9 homolog 1) (Su(var)3-9 homolog 1); (2582:) Histone-lysine N-methyltransferase, H3 lysine-9 specific 3 (HistoneH3-K9 methyltransferase 3) (H3-K9-HMTase 3) (Euchromatichistone-lysine N-methyltransferase 2) (HLA-B-associated transcript8) (Protein G9a); (2583:) Histone-lysine N-methyltransferase, H3 lysine-9 specific 5 (HistoneH3-K9 methyltransferase 5) (H3-K9-HMTase 5) (Euchromatichistone-lysine N-methyltransferase 1) (Eu-HMTase1) (G9a-likeprotein 1) (GLP1); (2584:) HIV-1 Tat interactive protein, 60kDa isoform 1 [Homo sapiens]; (2585:) HIV-1 Tat interactive

protein, 60kDa isoform 2 [Homo sapiens]; (2586:) HIV-1 Tat interactive protein, 60kDa isoform 3 [Homo sapiens]; (2587:) HLA class II histocompatibility antigen, DP alpha chain precursor(HLA-SB alpha chain) (MHC class II DP3-alpha) (DP(W3)) (DP(W4)); (2588:) HLA-B associated transcript 8 isoform a [Homo sapiens]; (2589:) HLA-B associated transcript 8 isoform b [Homo sapiens]; (2590:) hla-dcalpha alpha 2 domain (partial) [Homo sapiens]; (2591:) hla-dralpha related alpha 2 domain [Homo sapiens]; (2592:) HMC chymase I [Homo sapiens]; (2593:) HMGCR protein [Homo sapiens]; (2594:) hMLH1 gene product; (2595:) HMT1 hnRNP methyltransferase-like 6 [Homo sapiens]; (2596:) hMYHalpha1 [Homo sapiens]; (2597:) hMYHalpha2 [Homo sapiens]; (2598:) hMYHalpha3 [Homo sapiens]; (2599:) hMYHalpha4 [Homo sapiens]; (2600:) hMYHbeta1 [Homo sapiens]; (2601:) hMYHbeta3 [Homo sapiens]; (2602:) hMYHbeta5 [Homo sapiens]; (2603:) hMYHgamma2 [Homo sapiens]; (2604:) hMYHgamma3 [Homo sapiens]; (2605:) hMYHgamma4 [Homo sapiens]; (2606:) HNF1-alpha dimerization cofactor [Homo sapiens]; (2607:) homogentisate 1,2-dioxygenase [Homo sapiens]; (2608:) "homogentisate 1,2-dioxygenase; HGO [Homo sapiens]."; (2609:) homogentisate dioxygenase [Homo sapiens]; (2610:) homolgue of yeast DNA repair and recombination enzyme (RAD52)gene; (2611:) homolog of yeast long chain polyunsaturated fatty acid elongatio[Homo sapiens]; (2612:) homolog of yeast mutL gene; (2613:) Hormone-sensitive lipase (HSL); (2614:) hormone-sensitive lipase [Homo sapiens]; (2615:) HOYS7 [Homo sapiens]; (2616:) hPMS7 [Homo sapiens]; (2617:) H-protein; (2618:) HSPC015 [Homo sapiens]; (2619:) HSPC140 [Homo sapiens]; (2620:) HSPC150 [Homo sapiens]; (2621:) HSPC153 [Homo sapiens]; (2622:) HSPC279 [Homo sapiens]; (2623:) HtrA serine peptidase 1 [Homo sapiens]; (2624:) human 26S proteasome subunit p97 [Homo sapiens]; (2625:) Human Arylsulfatase A; (2626:) human endothelin-converting enzyme-1 d isoform [Homo sapiens]; (2627:) human gamma-glutamyl hydrolase [Homo sapiens]; (2628:) Human Glutathione Reductase A34e, R37w Mutant, Mixed DisulfideBetween Trypanothione And The Enzyme; (2629:) Human Glutathione Reductase A34e, R37w Mutant, Oxidized GlutathioneComplex; (2630:) Human Glutathione Reductase A34e, R37w Mutant, OxidizedTrypanothione Complex; (2631:) Human Glutathione Reductase A34e, R37w Mutant,Glutathionylspermidine Complex; (2632:) Human Glutathione Reductase A34eR37W MUTANT; (2633:) Human Glutathione Reductase Modified By Dinitrosoglutathione; (2634:) Human Glutathione Reductase Modified ByDiglutathione-Dinitroso-Iron; (2635:) human homolog of E. coli mutL gene product, Swiss-Prot AccessionNumber P23367; (2636:) human mammary

dihydrolipoamide acetyltransferase, mature sequence[Homo sapiens]; (2637:) Human Ubc9; (2638:) human ubiquitin conjugating enzyme G2 EC 6.3.2.19. [Homo sapiens]; (2639:) huntingtin [Homo sapiens]; (2640:) huntingtin interacting protein 2 [Homo sapiens]; (2641:) huntingtin interacting protein; (2642:) hyaluronan synthase (EC 2.4.1.-) - human; (2643:) hyaluronan synthase 3 [Homo sapiens]; (2644:) Hyaluronidase-2 precursor (Hyal-2) (Hyaluronoglucosaminidase-2)(LUCA-2); (2645:) hyaluronoglucosaminidase 1 isoform 1 [Homo sapiens]; (2646:) hyaluronoglucosaminidase 1 isoform 2 [Homo sapiens]; (2647:) hyaluronoglucosaminidase 1 isoform 3 [Homo sapiens]; (2648:) hyaluronoglucosaminidase 1 isoform 4 [Homo sapiens]; (2649:) hyaluronoglucosaminidase 1 isoform 5 [Homo sapiens]; (2650:) hyaluronoglucosaminidase 1 isoform 6 [Homo sapiens]; (2651:) hydroxyacyl glutathione hydrolase isoform 1 [Homo sapiens]; (2652:) hydroxyacyl glutathione hydrolase isoform 2 [Homo sapiens]; (2653:) hydroxyacyl-Coenzyme A dehydrogenase, type II isoform 1 [Homosapiens]; (2654:) hydroxyacyl-Coenzyme A dehydrogenase, type II isoform 2 [Homosapiens]; (2655:) hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroiddelta-isomerase 1 [Homo sapiens]; (2656:) hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroiddelta-isomerase 2 [Homo sapiens]; (2657:) Hydroxymethylbilane synthase [Homo sapiens]; (2658:) hydroxymethylbilane synthase isoform 1 [Homo sapiens]; (2659:) hydroxymethylbilane synthase isoform 2 [Homo sapiens]; (2660:) hydroxymethylbilane synthase; (2661:) Hydroxymethylglutaryl-CoA synthase, cytoplasmic (HMG-CoA synthase)(3-hydroxy-3-methylglutaryl coenzyme A synthase); (2662:) Hydroxymethylglutaryl-CoA synthase, mitochondrial precursor(HMG-CoA synthase) (3-hydroxy-3-methylglutaryl coenzyme Asynthase); (2663:) hydroxyprostaglandin dehydrogenase 15-(NAD) [Homo sapiens]; (2664:) hydroxysteroid (11-beta) dehydrogenase 2 [Homo sapiens]; (2665:) hydroxysteroid (17-beta) dehydrogenase 1 [Homo sapiens]; (2666:) hydroxysteroid (17-beta) dehydrogenase 2 [Homo sapiens]; (2667:) hydroxysteroid (17-beta) dehydrogenase 4 [Homo sapiens]; (2668:) hydroxysteroid (17-beta) dehydrogenase 7 [Homo sapiens]; (2669:) hypoxanthine phosphoribosyltransferase [Homo sapiens]; (2670:) hypoxanthine phosphoribosyltransferase 1 [Homo sapiens]; (2671:) Hypoxanthine-guanine phosphoribosyltransferase (HGPRT) (HGPRTase); (2672:) Hypoxia-inducible factor 1 alpha (HIF-1 alpha) (HIF1 alpha)(ARNT-interacting protein) (Member of PAS protein 1) (MOP1); (2673:) Hypoxia-inducible factor 1 alpha inhibitor (Hypoxia-induciblefactor asparagine hydroxylase) (Factor inhibiting HIF-1)

(FIH-1); (2674:) hypoxia-inducible factor 1, alpha subunit inhibitor [Homo sapiens]; (2675:) hypoxia-inducible factor 1, alpha subunit isoform 1 [Homo sapiens]; (2676:) hypoxia-inducible factor 1, alpha subunit isoform 2 [Homo sapiens]; (2677:) I beta 1-6 N-acetylglucosaminyltransferase; (2678:) I beta-1,6-N-acetylglucosaminyltransferase A form [Homo sapiens]; (2679:) I beta-1,6-N-acetylglucosaminyltransferase B form [Homo sapiens]; (2680:) I beta-1,6-N-acetylglucosaminyltransferase C form [Homo sapiens]; (2681:) IARS2 protein [Homo sapiens]; (2682:) "i-beta-1,3-N-acetylglucosaminyltransferase;poly-N-acetyllactosamine extension enzyme i-antigen; iGnT [Homosapiens]."; (2683:) I-branching beta-1,6-acetylglucosaminyltransferase familypolypeptide 1 [Homo sapiens]; (2684:) I-branching beta-1,6-acetylglucosaminyltransferase familypolypeptide 2 [Homo sapiens]; (2685:) I-branching beta-1,6-acetylglucosaminyltransferase familypolypeptide 3 [Homo sapiens]; (2686:) I-branching enzyme [Homo sapiens]; (2687:) ICE-LAP6 - human; (2688:) ICE-LAP6; (2689:) ICH-1L; (2690:) ICH-1S; (2691:) Ich-2; (2692:) "Iduronate 2-sulfatase precursor (Alpha-L-iduronate sulfatesulfatase) (Idursulfase) [Contains:) Iduronate 2-sulfatase 42 kDachain; Iduronate 2-sulfatase 14 kDa chain]."; (2693:) iduronate 2-sulfatase; (2694:) I-FLICE [Homo sapiens]; (2695:) I-FLICE isoform 2 [Homo sapiens]; (2696:) I-FLICE isoform 3 [Homo sapiens]; (2697:) I-FLICE isoform 4 [Homo sapiens]; (2698:) I-FLICE isoform 5 [Homo sapiens]; (2699:) IgG receptor FcRn large subunit p51 precursor (FcRn) (Neonatal Fcreceptor) (IgG Fc fragment receptor transporter, alpha chain); (2700:) IKK-related kinase epsilon [Homo sapiens]; (2701:) IlvB (bacterial acetolactate synthase)-like [Homo sapiens]; (2702:) ilvB (bacterial acetolactate synthase)-like isoform 1 [Homosapiens]; (2703:) ilvB (bacterial acetolactate synthase)-like isoform 1 variant [Homosapiens]; (2704:) ilvB (bacterial acetolactate synthase)-like isoform 2 [Homosapiens]; (2705:) immunodeficiency virus type 1, HIV-1 gp120 - human (fragments); (2706:) Immunoglobulin alpha Fc receptor precursor (IgA Fc receptor) (CD89antigen); (2707:) Immunoglobulin-like domain-containing receptor 1 precursor; (2708:) Importin-11 (Imp11) (Ran-binding protein 11) (RanBP11); (2709:) Inactive ubiquitin carboxyl-terminal hydrolase 50 (Inactiveubiquitin-specific peptidase 50); (2710:) indoleamine-pyrrole 2,3 dioxygenase [Homo sapiens]; (2711:) indolethylamine N-methyltransferase [Homo sapiens]; (2712:) inducible nitric oxide synthase; (2713:) inhibin alpha subunit precursor [Homo sapiens]; (2714:) inhibin beta A precursor [Homo sapiens]; (2715:) inhibin beta B subunit precursor [Homo sapiens]; (2716:) inhibitor of kappa light polypeptide gene enhancer in B-cells,kinase beta [Homo

sapiens]; (2717:) inhibitor of kappa light polypeptide gene enhancer in B-cells,kinase gamma [Homo sapiens]; (2718:) Inhibitor of nuclear factor kappa-B kinase alpha subunit (I kappa-Bkinase alpha) (IkBKA) (IKK-alpha) (IKK-A) (IkappaB kinase)(I-kappa-B kinase 1) (IKK1) (Conserved helix-loop-helix ubiquitouskinase) (Nuclear factor NF-kappa-B inhibitor kinase alpha)(NFKBIKA); (2719:) Inner Lipoyl Domain From Human Pyruvate Dehydrogenase (Pdh)Complex, Nmr, 1 Structure; (2720:) Inorganic pyrophosphatase (Pyrophosphate phospho-hydrolase)(PPase); (2721:) Inorganic pyrophosphatase 2, mitochondrial precursor (PPase 2)(Pyrophosphatase SID6-306); (2722:) inosine monophosphate dehydrogenase 2 [Homo sapiens]; (2723:) Inosine triphosphate pyrophosphatase (ITPase) (Inosinetriphosphatase) (Putative oncogene protein hlc14-06-p); (2724:) Inosine-5'-monophosphate dehydrogenase 1 (IMP dehydrogenase 1)(IMPDH-I) (IMPD 1); (2725:) Inosine-5'-monophosphate dehydrogenase 2 (IMP dehydrogenase 2)(IMPDH-II) (IMPD 2); (2726:) inositol 1,3,4,5,6-pentakisphosphate 2-kinase [Homo sapiens]; (2727:) inositol 1,3,4-triphosphate 5/6 kinase [Homo sapiens]; (2728:) inositol 1,3,4-trisphosphate 5/6-kinase; (2729:) inositol 1,4,5-triphosphate receptor, type 3 [Homo sapiens]; (2730:) inositol 1,4,5-trisphosphate 3-kinase B - human; (2731:) Inositol 1,4,5-trisphosphate receptor type 1 (Type 1 inositol1,4,5-trisphosphate receptor) (Type 1 InsP3 receptor) (IP3 receptorisoform 1) (InsP3R1) (IP3R); (2732:) Inositol 1,4,5-trisphosphate receptor type 2 (Type 2 inositol1,4,5-trisphosphate receptor) (Type 2 InsP3 receptor) (IP3 receptorisoform 2) (InsP3R2); (2733:) Inositol 1,4,5-trisphosphate receptor type 3 (Type 3 inositol1,4,5-trisphosphate receptor) (Type 3 InsP3 receptor) (IP3 receptorisoform 3) (InsP3R3); (2734:) Inositol Monophosphatase (E.C.3.1.3.25) (Apoenzyme); (2735:) Inositol monophosphatase (IMPase) (IMP) (Inositol-1(or4)-monophosphatase) (Lithium-sensitive myo-inositol monophosphataseA1); (2736:) Inositol monophosphatase 2 (IMPase 2) (IMP 2) (Inositol-1(or4)-monophosphatase 2) (Myo-inositol monophosphatase A2); (2737:) Inositol polyphosphate 1-phosphatase (IPPase) (IPP); (2738:) inositol polyphosphate-1-phosphatase [Homo sapiens]; (2739:) inositol polyphosphate-4-phosphatase, type 1 isoform a [Homosapiens]; (2740:) inositol polyphosphate-4-phosphatase, type 1 isoform b [Homosapiens]; (2741:) inositol polyphosphate-4-phosphatase, type II, 105kD [Homosapiens]; (2742:) inositol(myo)-1(or 4)-monophosphatase 1 [Homo sapiens]; (2743:) Inositol-pentakisphosphate 2-kinase(Inositol-1,3,4,5,6-pentakisphosphate 2-kinase) (Ins(1,3,4,5,6)P52-kinase) (InsP5 2-kinase) (IPK1 homolog); (2744:) Inositol-tetrakisphosphate 1-kinase (Inositol-triphosphate5/6-kinase) (Inositol 1,3,4-trisphosphate 5/6-kinase); (2745:)

Inositol-trisphosphate 3-kinase A (Inositol 1,4,5-trisphosphate3-kinase A) (IP3K A) (IP3 3-kinase A); (2746:) Inositol-trisphosphate 3-kinase B (Inositol 1,4,5-trisphosphate3-kinase B) (IP3K B) (IP3 3-kinase B) (IP3K-B); (2747:) Inositol-trisphosphate 3-kinase C (Inositol 1,4,5-trisphosphate3-kinase C) (InsP 3-kinase C) (IP3K-C); (2748:) insulin receptor [Homo sapiens]; (2749:) "Insulin receptor precursor (IR) (CD220 antigen) [Contains:) Insulinreceptor subunit alpha; Insulin receptor subunit beta]."; (2750:) insulin receptor substrate 1 [Homo sapiens]; (2751:) "Insulin receptor-related protein precursor (IRR) (IR-relatedreceptor) [Contains:) Insulin receptor-related protein alpha chain;Insulin receptor-related protein beta chain]."; (2752:) insulin receptor-related receptor - human (fragment); (2753:) Insulin-degrading enzyme (Insulysin) (Insulinase) (Insulinprotease); (2754:) Insulin-degrading enzyme [Homo sapiens]; (2755:) insulin-like growth factor 1 (somatomedin C) [Homo sapiens]; (2756:) "Insulin-like growth factor 1 receptor precursor (Insulin-likegrowth factor I receptor) (IGF-I receptor) (CD221 antigen)[Contains:) Insulin-like growth factor 1 receptor alpha chain;Insulin-like growth factor 1 receptor beta chain]."; (2757:) insulin-like growth factor 2 [Homo sapiens]; (2758:) insulin-like growth factor 2 receptor [Homo sapiens]; (2759:) insulysin [Homo sapiens]; (2760:) Integral membrane protein 2B (Transmembrane protein BRI) [Contains:ABri/ADan amyloid peptide]; (2761:) Integral membrane protein 2C (Transmembrane protein BRI3) (Cerebralprotein 14) [Contains:) CT-BRI3]; (2762:) integral membrane protein 2C isoform 1 [Homo sapiens]; (2763:) integral membrane protein 2C isoform 2 [Homo sapiens]; (2764:) integral membrane protein 2C isoform 3 [Homo sapiens]; (2765:) Integral membrane protein DGCR2/IDD precursor; (2766:) integrin alpha chain, alpha 6 [Homo sapiens]; (2767:) Integrin alpha-1 (Laminin and collagen receptor) (VLA-1) (CD49aantigen); (2768:) Integrin alpha-10 precursor; (2769:) Integrin alpha-11 precursor; (2770:) Integrin alpha-2 precursor (Platelet membrane glycoprotein Ia)(GPIa) (Collagen receptor) (VLA-2 alpha chain) (CD49b antigen); (2771:) "Integrin alpha-3 precursor (Galactoprotein B3) (GAPB3) (VLA-3 alphachain) (FRP-2) (CD49c antigen) [Contains:) Integrin alpha-3 heavychain; Integrin alpha-3 light chain]."; (2772:) Integrin alpha-4 precursor (Integrin alpha-IV) (VLA-4) (CD49dantigen); (2773:) "Integrin alpha-5 precursor (Fibronectin receptor subunit alpha)(Integrin alpha-F) (VLA-5) (CD49e antigen) [Contains:) Integrinalpha-5 heavy chain; Integrin alpha-5 light chain]."; (2774:) "Integrin alpha-6 precursor (VLA-6) (CD49f antigen) [Contains:Integrin alpha-6 heavy chain; Integrin alpha-6 light chain]."; (2775:) "Integrin alpha-7 precursor [Contains:) Integrin alpha-7 heavy chain;Integrin alpha-7

light chain]."; (2776:) "Integrin alpha-8 precursor [Contains:) Integrin alpha-8 heavy chain;Integrin alpha-8 light chain]."; (2777:) Integrin alpha-9 precursor (Integrin alpha-RLC); (2778:) Integrin alpha-D precursor (Leukointegrin alpha D) (ADB2) (CD11dantigen); (2779:) "Integrin alpha-E precursor (Mucosal lymphocyte 1 antigen) (HML-1antigen) (Integrin alpha-IEL) (CD103 antigen) [Contains:) Integrinalpha-E light chain; Integrin alpha-E heavy chain]."; (2780:) "Integrin alpha-IIb precursor (Platelet membrane glycoprotein IIb)(GPalpha IIb) (GPIIb) (CD41 antigen) [Contains:) Integrin alpha-IIbheavy chain; Integrin alpha-IIb light chain]."; (2781:) Integrin alpha-L precursor (Leukocyte adhesion glycoprotein LFA-1alpha chain) (LFA-1A) (Leukocyte function-associated molecule 1alpha chain) (CD11a antigen); (2782:) Integrin alpha-M precursor (Cell surface glycoprotein MAC-1 alphasubunit) (CR-3 alpha chain) (Leukocyte adhesion receptor MO1)(Neutrophil adherence receptor) (CD11b antigen); (2783:) "Integrin alpha-V precursor (Vitronectin receptor subunit alpha)(CD51 antigen) [Contains:) Integrin alpha-V heavy chain; Integrinalpha-V light chain]."; (2784:) Integrin alpha-X precursor (Leukocyte adhesion glycoprotein p150,95alpha chain) (Leukocyte adhesion receptor p150,95) (Leu M5) (CD11cantigen); (2785:) Integrin beta 1 binding protein 3 [Homo sapiens]; (2786:) integrin beta 1 binding protein 3 isoform 2 [Homo sapiens]; (2787:) Integrin beta-1 precursor (Fibronectin receptor subunit beta)(Integrin VLA-4 subunit beta) (CD29 antigen); (2788:) Integrin beta-2 precursor (Cell surface adhesion glycoproteinsLFA-1/CR3/p150,95 subunit beta) (Complement receptor C3 subunitbeta) (CD18 antigen); (2789:) Integrin beta-3 precursor (Platelet membrane glycoprotein IIIa)(GPIIIa) (CD61 antigen); (2790:) Integrin beta-4 precursor (GP150) (CD104 antigen); (2791:) Integrin beta-5 precursor; (2792:) Integrin beta-6 precursor; (2793:) Integrin beta-7 precursor; (2794:) Integrin beta-8 precursor; (2795:) integrin-linked kinase [Homo sapiens]; (2796:) Integrin-linked protein kinase 1 (ILK-1) (59 kDaserine/threonine-protein kinase) (p59ILK); (2797:) inter-alpha globulin inhibitor H2 polypeptide [Homo sapiens]; (2798:) intercellular adhesion molecule 1 precursor [Homo sapiens]; (2799:) interferon, gamma [Homo sapiens]; (2800:) interferon, gamma-inducible protein 30 preproprotein [Homosapiens]; (2801:) Interferon-alpha/beta receptor alpha chain precursor(IFN-alpha-REC); (2802:) Interferon-alpha/beta receptor beta chain precursor (IFN-alpha-REC)(Type I interferon receptor) (IFN-R) (Interferon alpha/betareceptor 2); (2803:) Interferon-gamma receptor alpha chain precursor (IFN-gamma-R1)(CD119 antigen) (CDw119); (2804:) Interferon-gamma receptor beta chain precursor (Interferon-gammareceptor accessory factor 1) (AF-1) (Interferon-gamma transducer1); (2805:)

Interferon-induced 17 kDa protein precursor [Contains:) Ubiquitincross-reactive protein (hUCRP) (Interferon-induced 15 kDaprotein)]; (2806:) Interferon-induced, double-stranded RNA-activated protein kinase(Interferon-inducible RNA-dependent protein kinase) (Protein kinaseRNA-activated) (PKR) (p68 kinase) (P1/eIF-2A protein kinase); (2807:) Interferon-stimulated gene 20 kDa protein (Promyelocytic leukemianuclear body-associated protein ISG20) (Estrogen-regulatedtranscript 45 protein); (2808:) interleukin 1 receptor antagonist isoform 1 precursor [Homosapiens]; (2809:) interleukin 1 receptor antagonist isoform 2 [Homo sapiens]; (2810:) interleukin 1 receptor antagonist isoform 3 [Homo sapiens]; (2811:) interleukin 1 receptor antagonist isoform 4 [Homo sapiens]; (2812:) interleukin 1, beta proprotein [Homo sapiens]; (2813:) interleukin 18 proprotein [Homo sapiens]; (2814:) interleukin 1-beta convertase [Homo sapiens]; (2815:) interleukin 1-beta convertase; (2816:) Interleukin 1-beta converting enzyme isoform beta; (2817:) Interleukin 1-beta converting enzyme isoform delta; (2818:) Interleukin 1-beta converting enzyme isoform epsilon; (2819:) interleukin 1-beta converting enzyme isoform gamma; (2820:) interleukin 1beta-converting enzyme; (2821:) interleukin 6 receptor isoform 1 precursor [Homo sapiens]; (2822:) interleukin 6 receptor isoform 2 precursor [Homo sapiens]; (2823:) interleukin 8 precursor [Homo sapiens]; (2824:) interleukin 8 receptor beta [Homo sapiens]; (2825:) interleukin-1 beta converting enzyme {N-terminal} [human, PeptidePartial, 23 aa]; (2826:) Interleukin-1 receptor accessory protein precursor (IL-1 receptoraccessory protein) (IL-1RAcP); (2827:) Interleukin-1 receptor type I precursor (IL-1R-1) (IL-1RT1)(IL-1R-alpha) (p80) (CD121a antigen); (2828:) Interleukin-1 receptor type II precursor (IL-1R-2) (IL-1R-beta)(CD121b antigen) (CDw121b); (2829:) Interleukin-1 receptor-associated kinase 1 (IRAK-1); (2830:) Interleukin-1 receptor-associated kinase-like 2 (IRAK-2); (2831:) Interleukin-1 receptor-like 1 precursor (ST2 protein); (2832:) Interleukin-1 receptor-like 2 precursor (IL-1Rrp2) (Interleukin-1receptor-related protein 2) (IL1R-rp2); (2833:) Interleukin-10 receptor alpha chain precursor (IL-10R-A) (IL-10R1)(CDw210a antigen); (2834:) Interleukin-10 receptor beta chain precursor (IL-10R-B) (IL-10R2)(Cytokine receptor family 2 member 4) (Cytokine receptor class-IImember 4) (CRF2-4) (CDw210b antigen); (2835:) Interleukin-11 receptor alpha chain precursor (IL-11R-alpha)(IL-11RA); (2836:) Interleukin-12 receptor beta-1 chain precursor (IL-12R-beta1)(Interleukin-12 receptor beta) (IL-12 receptor beta component)(IL-12RB1) (CD212 antigen); (2837:) Interleukin-12 receptor beta-2 chain precursor (IL-12 receptorbeta-2) (IL-12R-beta2); (2838:) Interleukin-13 receptor alpha-1 chain precursor (IL-13R-alpha-1)(IL-13RA-1) (CD213a1 antigen);

(2839:) Interleukin-13 receptor alpha-2 chain precursor(Interleukin-13-binding protein) (CD213a2 antigen); (2840:) Interleukin-15 receptor alpha chain precursor (IL-15R-alpha)(IL-15RA); (2841:) Interleukin-17 receptor A precursor (IL-17 receptor) (CD217antigen) (CDw217); (2842:) Interleukin-17 receptor B precursor (IL-17 receptor B) (IL-17RB)(Interleukin-17B receptor) (IL-17B receptor) (IL-17 receptorhomolog 1) (IL-17Rh1) (IL17Rh1) (Cytokine receptor CRL4); (2843:) Interleukin-17 receptor C precursor (IL-17 receptor C) (IL-17RC)(Interleukin-17 receptor-like protein) (IL-17RL) (Interleukin-17receptor homolog) (IL17Rhom); (2844:) Interleukin-17 receptor D precursor (IL-17 receptor D) (IL-17RD)(Interleukin-17D receptor) (IL-17D receptor) (IL17Rhom)(Interleukin-17 receptor-like protein) (Sef homolog) (hSef); (2845:) Interleukin-18 receptor 1 precursor (IL1 receptor-related protein)(IL-1Rrp) (CDw218a antigen); (2846:) Interleukin-18 receptor accessory protein precursor (IL-18 receptoraccessory protein) (IL-18RAcP) (Interleukin-18 receptor accessoryprotein-like) (IL-18Rbeta) (IL-1R accessory protein-like)(IL-1RAcPL) (Accessory protein-like) (AcPL) (IL-1R7) (CDw218bantigen); (2847:) interleukin-1B converting enzyme [Homo sapiens]; (2848:) Interleukin-2 receptor alpha chain precursor (IL-2 receptor alphasubunit) (IL-2-RA) (IL2-RA) (p55) (TAC antigen) (CD25 antigen); (2849:) Interleukin-2 receptor subunit beta precursor (IL-2 receptor)(P70-75) (p75) (High affinity IL-2 receptor subunit beta) (CD122antigen); (2850:) Interleukin-20 receptor alpha chain precursor (IL-20R-alpha)(IL-20R1) (Cytokine receptor family 2 member 8) (Cytokine receptorclass-II member 8) (CRF2-8) (ZcytoR7); (2851:) Interleukin-20 receptor beta chain precursor (IL-20R-beta)(IL-20R2); (2852:) Interleukin-21 receptor precursor (IL-21R) (Novel interleukinreceptor); (2853:) Interleukin-22 receptor alpha-2 chain precursor (IL-22R-alpha-2)(Interleukin 22-binding protein) (IL22BP) (Cytokine receptor familyclass II member 10) (CRF2-10) (Cytokine receptor family type 2,soluble 1) (CRF2-S1); (2854:) Interleukin-27 receptor alpha chain precursor (IL-27R-alpha)(WSX-1) (Type I T-cell cytokine receptor) (TCCR) (Protein CRL1); (2855:) Interleukin-28 receptor alpha chain precursor (IL-28R-alpha)(IL-28RA) (Cytokine receptor family 2 member 12) (Cytokine receptorclass-II member 12) (CRF2-12) (Interferon lambda receptor 1)(IFN-lambda R1) (Likely interleukin or cytokine receptor 2); (2856:) Interleukin-3 receptor alpha chain precursor (IL-3R-alpha) (CD123antigen); (2857:) Interleukin-4 receptor alpha chain precursor (IL-4R-alpha) (CD124antigen) [Contains:) Soluble interleukin-4 receptor alpha chain(sIL4Ralpha/prot) (IL-4-binding protein) (IL4-BP)]; (2858:) Interleukin-5 receptor alpha chain precursor (IL-5R-alpha) (CD125antigen) (CDw125); (2859:)

Interleukin-6 receptor alpha chain precursor (IL-6R-alpha) (IL-6R1) (Membrane glycoprotein 80) (gp80) (CD126 antigen); (2860:) Interleukin-6 receptor subunit beta precursor (IL-6R-beta)(Interleukin-6 signal transducer) (Membrane glycoprotein 130)(gp130) (Oncostatin-M receptor alpha subunit) (CD130 antigen)(CDw130); (2861:) Interleukin-7 receptor alpha chain precursor (IL-7R-alpha) (CD127antigen) (CDw127); (2862:) Interleukin-9 receptor precursor (IL-9R) (CD129 antigen); (2863:) Interphotoreceptor matrix proteoglycan 1 precursor(Interphotoreceptor matrix proteoglycan of 150 kDa) (IPM-150)(Sialoprotein associated with cones and rods); (2864:) "Interstitial collagenase precursor (Matrix metalloproteinase-1)(MMP-1) (Fibroblast collagenase) [Contains:) 22 kDa interstitialcollagenase; 27 kDa interstitial collagenase]."; (2865:) intestinal alkaline phosphatase precursor [Homo sapiens]; (2866:) intestinal alkaline sphingomyelinase [Homo sapiens]; (2867:) iron-sulfur cluster assembly enzyme isoform ISCU1 [Homo sapiens]; (2868:) iron-sulfur cluster assembly enzyme isoform ISCU2 precursor [Homosapiens]; (2869:) islet amyloid polypeptide precursor [Homo sapiens]; (2870:) Isocitrate dehydrogenase [NAD] subunit gamma, mitochondrialprecursor (Isocitric dehydrogenase) (NAD(+)-specific ICDH); (2871:) Isocitrate dehydrogenase [NADP] cytoplasmic (CytosolicNADP-isocitrate dehydrogenase) (Oxalosuccinate decarboxylase) (IDH)(NADP(+)-specific ICDH) (IDP); (2872:) isocitrate dehydrogenase 1 (NADP+), soluble [Homo sapiens]; (2873:) isocitrate dehydrogenase 3 (NAD+) alpha precursor [Homo sapiens]; (2874:) isopentenyl-diphosphate delta isomerase [Homo sapiens]; (2875:) isopeptidase T; (2876:) isopeptidase T-3 [Homo sapiens]; (2877:) isoprenylcysteine carboxyl methyltransferase [Homo sapiens]; (2878:) isovaleryl Coenzyme A dehydrogenase [Homo sapiens]; (2879:) Itchy homolog E3 ubiquitin protein ligase (Itch)(Atrophin-1-interacting protein 4) (AIP4) (NFE2-associatedpolypeptide 1) (NAPP1); (2880:) Janus kinase 3 [Homo sapiens]; (2881:) JmjC domain-containing histone demethylation protein 1B([Histone-H3]-lysine-36 demethylase 1B) (F-box/LRR-repeat protein10) (F-box and leucine-rich repeat protein 10) (F-box proteinFBL10) (Protein JEMMA) (Jumonji domain-containing EMSY-interactormethyltransferase motif protein) (CXXC-type zinc finger protein 2)(Protein-containing CXXC domain 2); (2882:) JmjC domain-containing histone demethylation protein 2B (Jumonjidomain-containing protein 1B) (Nuclear protein 5qNCA); (2883:) JmjC domain-containing histone demethylation protein 3B (Jumonjidomain-containing protein 2B); (2884:) JmjC domain-containing histone demethylation protein 3C (Jumonjidomain-containing protein 2C) (Gene amplified in squamous cellcarcinoma 1 protein) (GASC-1 protein); (2885:) JmjC domain-containing histone demethylation protein 3D

(Jumonjidomain-containing protein 2D); (2886:) JRK protein [Homo sapiens]; (2887:) jub, ajuba homolog isoform 1 [Homo sapiens]; (2888:) jub, ajuba homolog isoform 2 [Homo sapiens]; (2889:) jun oncogene [Homo sapiens]; (2890:) junction plakoglobin [Homo sapiens]; (2891:) JUP protein [Homo sapiens]; (2892:) kalirin, RhoGEF kinase isoform 1 [Homo sapiens]; (2893:) kalirin, RhoGEF kinase isoform 2 [Homo sapiens]; (2894:) kalirin, RhoGEF kinase isoform 3 [Homo sapiens]; (2895:) kallikrein 8 isoform 1 preproprotein [Homo sapiens]; (2896:) kallikrein 8 isoform 2 [Homo sapiens]; (2897:) kallikrein 8 isoform 3 [Homo sapiens]; (2898:) kallikrein 8 isoform 4 [Homo sapiens]; (2899:) Kallikrein-5 precursor (Stratum corneum tryptic enzyme)(Kallikrein-like protein 2) (KLK-L2); (2900:) Kallikrein-6 precursor (Protease M) (Neurosin) (Zyme) (SP59); (2901:) Kallikrein-7 precursor (hK7) (Stratum corneum chymotryptic enzyme)(hSCCE); (2902:) kallikrein-related peptidase 4 preproprotein [Homo sapiens]; (2903:) kallikrein-related peptidase 5 preproprotein [Homo sapiens]; (2904:) kallikrein-related peptidase 6 isoform A preproprotein [Homosapiens]; (2905:) kallikrein-related peptidase 6 isoform B [Homo sapiens]; (2906:) Kallistatin precursor (Serpin A4) (Kallikrein inhibitor) (Proteaseinhibitor 4); (2907:) Kappa-type opioid receptor (KOR-1); (2908:) KAT3 protein [Homo sapiens]; (2909:) Katanin p60 ATPase-containing subunit A1 (Katanin p60 subunit A1)(p60 katanin); (2910:) katanin p60 subunit A 1 [Homo sapiens]; (2911:) katanin p80 subunit B 1 [Homo sapiens]; (2912:) KDEL (Lys-Asp-Glu-Leu) containing 1 [Homo sapiens]; (2913:) KDEL (Lys-Asp-Glu-Leu) containing 2 [Homo sapiens]; (2914:) KDEL motif-containing protein 1 precursor; (2915:) KDEL motif-containing protein 2 precursor; (2916:) Kelch-like ECH-associated protein 1 (Cytosolic inhibitor of Nrf2)(Kelch-like protein 19); (2917:) Kell blood group, metallo-endopeptidase [Homo sapiens]; (2918:) keratan sulfate Gal-6-sulfotransferase [Homo sapiens]; (2919:) Ketohexokinase (Hepatic fructokinase); (2920:) Ketosamine-3-kinase (Fructosamine-3-kinase-related protein); (2921:) KH-type splicing regulatory protein (FUSE binding protein 2) [Homosapiens]; (2922:) kidney and liver proline oxidase 1 [Homo sapiens]; (2923:) Killer cell immunoglobulin-like receptor 2DL1 precursor (MHC classI NK cell receptor) (Natural killer-associated transcript 1)(NKAT-1) (p58 natural killer cell receptor clones CL-42/47.11) (p58NK receptor) (p58.1 MHC class-I-specific NK receptor) (CD158aantigen); (2924:) Killer cell immunoglobulin-like receptor 2DL2 precursor (MHC classI NK cell receptor) (Natural killer-associated transcript 6)(NKAT-6) (p58 natural killer cell receptor clone CL-43) (p58 NKreceptor); (2925:) Killer cell immunoglobulin-like receptor 2DL3 precursor (MHC classI NK cell receptor) (Natural killer-associated transcript 2)(NKAT-2) (NKAT2a)

(NKAT2b) (p58 natural killer cell receptor cloneCL-6) (p58 NK receptor) (p58.2 MHC class-I-specific NK receptor)(Killer inhibitory receptor cl 2-3) (KIR-023GB) (CD158b antigen); (2926:) Killer cell immunoglobulin-like receptor 2DL4 precursor (MHC classI NK cell receptor KIR103AS) (Killer cell inhibitory receptor103AS) (KIR-103AS) (G9P) (CD158d antigen); (2927:) Killer cell immunoglobulin-like receptor 2DS1 precursor (MHC classI NK cell receptor Eb6 ActI) (CD158h antigen); (2928:) Killer cell immunoglobulin-like receptor 2DS2 precursor (MHC classI NK cell receptor) (Natural killer-associated transcript 5)(NKAT-5) (p58 natural killer cell receptor clone CL-49) (p58 NKreceptor) (NK receptor 183 ActI) (CD158j antigen); (2929:) Killer cell immunoglobulin-like receptor 2DS3 precursor (MHC classI NK cell receptor) (Natural killer-associated transcript 7)(NKAT-7); (2930:) Killer cell immunoglobulin-like receptor 2DS4 precursor (MHC classI NK cell receptor) (Natural killer-associated transcript 8)(NKAT-8) (P58 natural killer cell receptor clone CL-39) (p58 NKreceptor) (CL-17) (CD158i antigen); (2931:) Killer cell immunoglobulin-like receptor 2DS5 precursor (MHC classI NK cell receptor) (Natural killer-associated transcript 9)(NKAT-9) (CD158g antigen); (2932:) Killer cell immunoglobulin-like receptor 3DL1 precursor (MHC classI NK cell receptor) (Natural killer-associated transcript 3)(NKAT-3) (p70 natural killer cell receptor clones CL-2/CL-11)(HLA-BW4-specific inhibitory NK cell receptor); (2933:) Killer cell immunoglobulin-like receptor 3DL2 precursor (MHC classI NK cell receptor) (Natural killer-associated transcript 4)(NKAT-4) (p70 natural killer cell receptor clone CL-5) (CD158kantigen); (2934:) Killer cell immunoglobulin-like receptor 3DL3 precursor (Killercell inhibitory receptor 1) (CD158z antigen); (2935:) Killer cell immunoglobulin-like receptor 3DS1 precursor (MHC classI NK cell receptor) (Natural killer-associated transcript 10)(NKAT-10); (2936:) Killer cell lectin-like receptor subfamily F member 1 (Lectin-likereceptor F1) (Activating coreceptor NKp80); (2937:) kinase insert domain receptor (a type III receptor tyrosine kinase)[Homo sapiens]; (2938:) kinase interacting stathmin [Homo sapiens]; (2939:) kinase related protein, telokin isoform 7 [Homo sapiens]; (2940:) kinase related protein, telokin isoform 8 [Homo sapiens]; (2941:) kinase,phosphoglycerate; (2942:) kinesin family member 23 isoform 1 [Homo sapiens]; (2943:) kinesin family member 23 isoform 2 [Homo sapiens]; (2944:) Kinesin-like protein KIF23 (Mitotic kinesin-like protein 1)(Kinesin-like protein 5); (2945:) Kinesin-like protein KIFC1 (Kinesin-like protein 2)(Kinesin-related protein HSET); (2946:) KiSS-1 receptor (KiSS-1R) (Kisspeptins receptor) (Metastinreceptor) (G-protein coupled receptor 54) (Hypogonadotropin-1)(hOT7T175); (2947:) KIAA0184 [Homo sapiens]; (2948:) KIAA0184 protein [Homo sapiens]; (2949:)

KIAA0377 splice variant 4 [Homo sapiens]; (2950:) KIAA0398 [Homo sapiens]; (2951:) KIAA0433 [Homo sapiens]; (2952:) KIAA0837 protein [Homo sapiens]; (2953:) KIAA0934 protein [Homo sapiens]; (2954:) KIAA1238 protein [Homo sapiens]; (2955:) KIAA1289 protein [Homo sapiens]; (2956:) KIAA1385 protein [Homo sapiens]; (2957:) KIAA1463 protein [Homo sapiens]; (2958:) KIAA1516 protein [Homo sapiens]; (2959:) KIAA1734 protein [Homo sapiens]; (2960:) KIAA1846 protein [Homo sapiens]; (2961:) KIAA1963 protein [Homo sapiens]; (2962:) KIAA1992 protein [Homo sapiens]; (2963:) Kruppel-like factor 4 (gut) [Homo sapiens]; (2964:) kynureninase (L-kynurenine hydrolase) isoform a [Homo sapiens]; (2965:) kynureninase (L-kynurenine hydrolase) isoform b [Homo sapiens]; (2966:) Kynureninase (L-kynurenine hydrolase); (2967:) Kynurenine 3-monooxygenase (Kynurenine 3-hydroxylase); (2968:) kynurenine aminotransferase III [Homo sapiens]; (2969:) kynurenine aminotransferase III isoform 1 [Homo sapiens]; (2970:) kynurenine aminotransferase III isoform 2 [Homo sapiens]; (2971:) L-3-hydroxyacyl-Coenzyme A dehydrogenase precursor [Homo sapiens]; (2972:) "Lactase-phlorizin hydrolase precursor (Lactase-glycosylceramidase)[Includes:) Lactase ; Phlorizin hydrolase]."; (2973:) lactase-phlorizin hydrolase preproprotein [Homo sapiens]; (2974:) lactate dehydrogenase A [Homo sapiens]; (2975:) Lactosylceramide 4-alpha-galactosyltransferase(Alpha-1,4-galactosyltransferase)(UDP-galactose:beta-D-galactosyl-beta1-R4-alpha-D-galactosyltransferase)(Alpha-1,4-N-acetylglucosaminyltransferase) (Alpha4Gal-T1)(Globotriaosylceramide synthase) (Gb3 synthase) (CD77 synthase)(P1/Pk synthase); (2976:) Lactoylglutathione lyase (Methylglyoxalase) (Aldoketomutase)(Glyoxalase I) (Glx I) (Ketone-aldehyde mutase)(S-D-lactoylglutathione methylglyoxal lyase); (2977:) laeverin [Homo sapiens]; (2978:) lambda-crystallin [Homo sapiens]; (2979:) Lambda-crystallin homolog; (2980:) Lamin-B receptor (Integral nuclear envelope inner membrane protein)(LMN2R); (2981:) laminin alpha 3 subunit isoform 1 [Homo sapiens]; (2982:) laminin alpha 3 subunit isoform 2 [Homo sapiens]; (2983:) laminin subunit beta 3 precursor [Homo sapiens]; (2984:) laminin, gamma 2 isoform a precursor [Homo sapiens]; (2985:) laminin, gamma 2 isoform b precursor [Homo sapiens]; (2986:) LANCL2 protein [Homo sapiens]; (2987:) lanthionine synthetase C-like protein 1 [Homo sapiens]; (2988:) Lariat debranching enzyme; (2989:) Latrophilin-1 precursor (Calcium-independent alpha-latrotoxinreceptor 1) (Lectomedin-2); (2990:) Latrophilin-2 precursor (Calcium-independent alpha-latrotoxinreceptor 2) (Latrophilin homolog 1) (Lectomedin-1); (2991:) Latrophilin-3 precursor (Calcium-independent alpha-latrotoxinreceptor 3) (Lectomedin-3); (2992:) LBP-32 [Homo sapiens]; (2993:)

LBP-9 [Homo sapiens]; (2994:) LCFA CoA ligase [Homo sapiens]; (2995:) leader-binding protein 32 isoform 1 [Homo sapiens]; (2996:) leader-binding protein 32 isoform 2 [Homo sapiens]; (2997:) Lecithin retinol acyltransferase (Phosphatidylcholine--retinolO-acyltransferase); (2998:) lecithin retinol acyltransferase [Homo sapiens]; (2999:) lecithin-cholesterol acyltransferase precursor [Homo sapiens]; (3000:) legumain preproprotein [Homo sapiens]; (3001:) legumaturain [Homo sapiens]; (3002:) leprecan-like 1 [Homo sapiens]; (3003:) leprecan-like 2 [Homo sapiens]; (3004:) Leptin receptor precursor (LEP-R) (OB receptor) (OB-R) (HuB219)(CD295 antigen); (3005:) leucine aminopeptidase 3 [Homo sapiens]; (3006:) leucine proline-enriched proteoglycan (leprecan) 1 [Homo sapiens]; (3007:) leucine-rich alpha-2-glycoprotein 1 [Homo sapiens]; (3008:) Leucine-rich repeat serine/threonine-protein kinase 1; (3009:) Leucine-rich repeat-containing G-protein coupled receptor 4precursor (G-protein coupled receptor 48); (3010:) Leucine-rich repeat-containing G-protein coupled receptor 5precursor (Orphan G-protein coupled receptor HG38) (G-proteincoupled receptor 49) (G-protein coupled receptor 67); (3011:) Leucine-rich repeat-containing G-protein coupled receptor 6(VTS20631); (3012:) leucyl aminopeptidase (EC 3.4.11.1) / prolyl aminopeptidase (EC3.4.11.5) - human (fragment); (3013:) Leucyl-cystinyl aminopeptidase (Cystinyl aminopeptidase)(Oxytocinase) (OTase) (Insulin-regulated membrane aminopeptidase)(Insulin-responsive aminopeptidase) (IRAP) (Placental leucineaminopeptidase) (P-LAP); (3014:) Leukemia inhibitory factor receptor precursor (LIF receptor)(LIF-R) (CD118 antigen); (3015:) Leukocyte elastase precursor (Elastase-2) (Neutrophil elastase)(PMN elastase) (Bone marrow serine protease) (Medullasin) (Humanleukocyte elastase) (HLE); (3016:) Leukocyte immunoglobulin-like receptor subfamily A member 1precursor (Leukocyte immunoglobulin-like receptor 6) (LIR-6) (CD85iantigen); (3017:) Leukocyte immunoglobulin-like receptor subfamily A member 2precursor (Leukocyte immunoglobulin-like receptor 7) (LIR-7)(Immunoglobulin-like transcript 1) (ILT-1) (CD85h antigen); (3018:) Leukocyte immunoglobulin-like receptor subfamily A member 3precursor (Leukocyte immunoglobulin-like receptor 4) (LIR-4)(Immunoglobulin-like transcript 6) (ILT-6) (Monocyte inhibitoryreceptor HM43/HM31) (CD85e antigen); (3019:) Leukocyte immunoglobulin-like receptor subfamily A member 4precursor (Immunoglobulin-like transcript 7) (ILT-7) (CD85gantigen); (3020:) Leukocyte immunoglobulin-like receptor subfamily B member 1precursor (Leukocyte immunoglobulin-like receptor 1) (LIR-1)(Immunoglobulin-like transcript 2) (ILT-2) (Monocyte/macrophageimmunoglobulin-

like receptor 7) (MIR-7) (CD85j antigen); (3021:) Leukocyte immunoglobulin-like receptor subfamily B member 2precursor (Leukocyte immunoglobulin-like receptor 2) (LIR-2)(Immunoglobulin-like transcript 4) (ILT-4) (Monocyte/macrophageimmunoglobulin-like receptor 10) (MIR-10) (CD85d antigen); (3022:) Leukocyte immunoglobulin-like receptor subfamily B member 3precursor (Leukocyte immunoglobulin-like receptor 3) (LIR-3)(Immunoglobulin-like transcript 5) (ILT-5) (Monocyte inhibitoryreceptor HL9) (CD85a antigen); (3023:) Leukocyte immunoglobulin-like receptor subfamily B member 4precursor (Leukocyte immunoglobulin-like receptor 5) (LIR-5)(Immunoglobulin-like transcript 3) (ILT-3) (Monocyte inhibitoryreceptor HM18) (CD85k antigen); (3024:) Leukocyte immunoglobulin-like receptor subfamily B member 5precursor (Leukocyte immunoglobulin-like receptor 8) (LIR-8) (CD85cantigen); (3025:) Leukocyte tyrosine kinase receptor precursor (Protein tyrosinekinase 1); (3026:) Leukocyte-associated immunoglobulin-like receptor 1 precursor(LAIR-1) (hLAIR1) (CD305 antigen); (3027:) Leukocyte-associated immunoglobulin-like receptor 2 precursor(LAIR-2) (CD306 antigen); (3028:) Leukotriene A-4 hydrolase (LTA-4 hydrolase) (Leukotriene A(4)hydrolase); (3029:) leukotriene A4 hydrolase [Homo sapiens]; (3030:) leukotriene A-4 hydrolase precursor; (3031:) Leukotriene A4 hydrolase, LTA4 hydrolase [human, B-lymphocyticcell line Raji, Peptide Partial, 21 aa]; (3032:) leukotriene A4 hydrolase; (3033:) leukotriene B4 receptor [Homo sapiens]; (3034:) Leukotriene B4 receptor 1 (LTB4-R 1) (P2Y purinoceptor 7) (P2Y7)(Chemoattractant receptor-like 1) (G-protein coupled receptor 16); (3035:) Leukotriene B4 receptor 2 (LTB4-R2) (Seven transmembrane receptorBLTR2) (Leukotriene B4 receptor BLT2) (LTB4 receptor JULF2); (3036:) leukotriene C4 synthase (EC 6.-.-.-) - human; (3037:) leukotriene C4 synthase [Homo sapiens]; (3038:) Lice2 alpha [Homo sapiens]; (3039:) Lice2 beta cysteine protease [Homo sapiens]; (3040:) Lice2 gamma cysteine protease [Homo sapiens]; (3041:) ligase III, DNA, ATP-dependent isoform alpha precursor [Homosapiens]; (3042:) ligase III, DNA, ATP-dependent isoform beta precursor [Homosapiens]; (3043:) Limb region 1 protein homolog (Differentiation-related gene 14protein); (3044:) lipase A precursor [Homo sapiens]; (3045:) lipase C precursor [Homo sapiens]; (3046:) Lipase member I precursor (Membrane-associated phosphatidicacid-selective phospholipase A1-beta) (mPA-PLA1 beta) (LPD lipase); (3047:) lipase, gastric [Homo sapiens]; (3048:) Lipid phosphate phosphohydrolase 1 (Phosphatidic acid phosphatase2a) (Phosphatidate phosphohydrolase type 2a) (PAP2a) (PAP-2a)(PAP2-alpha); (3049:) Lipid phosphate phosphohydrolase 2 (Phosphatidic acid phosphatase2c) (Phosphatidate

phosphohydrolase type 2c) (PAP2c) (PAP-2c)(PAP2-gamma) (PAP2-G); (3050:) Lipid phosphate phosphohydrolase 3 (Phosphatidic acid phosphatase2b) (Phosphatidate phosphohydrolase type 2b) (PAP2b) (PAP-2b)(PAP2-beta) (Vascular endothelial growth factor and type Icollagen-inducible protein) (VCIP); (3051:) lipin 1 [Homo sapiens]; (3052:) Lipoamide acyltransferase component of branched-chain alpha-ketoacid dehydrogenase complex, mitochondrial precursor(Dihydrolipoyllysine-residue (2-methylpropanoyl)transferase) (E2)(Dihydrolipoamide branched chain transacylase) (BCKAD E2 subunit); (3053:) lipocalin 2 [Homo sapiens]; (3054:) Lipolysis-stimulated lipoprotein receptor; (3055:) Lipoprotein lipase precursor (LPL); (3056:) lipoprotein lipase precursor [Homo sapiens]; (3057:) lipoprotein Lp(a) precursor [Homo sapiens]; (3058:) lipoyl-containing component X [Homo sapiens]; (3059:) lipoyltransferase [Homo sapiens]; (3060:) lipoyltransferase 1 [Homo sapiens]; (3061:) Lipoyltransferase 1, mitochondrial precursor (Lipoate-proteinligase) (Lipoate biosynthesis protein) (Lipoyl ligase); (3062:) Liver carboxylesterase 1 precursor (Acyl coenzyme A:cholesterolacyltransferase) (ACAT) (Monocyte/macrophage serine esterase)(HMSE) (Serine esterase 1) (Brain carboxylesterase hBr1)(Triacylglycerol hydrolase) (TGH) (Egasyn); (3063:) liver phosphofructokinase isoform a [Homo sapiens]; (3064:) liver phosphofructokinase isoform a variant [Homo sapiens]; (3065:) liver phosphofructokinase isoform b [Homo sapiens]; (3066:) liver-type 1-phosphofructokinase [Homo sapiens]; (3067:) long chain fatty acyl CoA synthetase 2 [Homo sapiens]; (3068:) long chain polyunsaturated fatty acid elongation enzyme [Homosapiens]; (3069:) long-chain acyl-CoA synthetase [Homo sapiens]; (3070:) long-chain acyl-CoA synthetase 5 [Homo sapiens]; (3071:) long-chain acyl-CoA synthetase; (3072:) Long-chain fatty acid transport protein 1 (Fatty acid transportprotein 1) (FATP-1) (Solute carrier family 27 member 1); (3073:) Long-chain fatty acid transport protein 3 (Fatty acid transportprotein 3) (FATP-3) (Very long-chain acyl-CoA synthetase homolog 3)(VLCS-3) (Solute carrier family 27 member 3); (3074:) Long-chain fatty acid transport protein 4 (Fatty acid transportprotein 4) (FATP-4) (Solute carrier family 27 member 4); (3075:) Long-chain fatty acid transport protein 6 (Fatty acid transportprotein 6) (FATP-6) (Very long-chain acyl-CoA synthetase homolog 1)(VLCSH1) (hVLCS-H1) (Fatty-acid-coenzyme A ligase, very long-chain2) (Solute carrier family 27 member 6); (3076:) Long-chain-fatty-acid--CoA ligase 1 (Long-chain acyl-CoA synthetase1) (LACS 1) (Palmitoyl-CoA ligase 1) (Long-chain fatty acid CoAligase 2) (Long-chain acyl-CoA synthetase 2) (LACS 2) (Acyl-CoAsynthetase 1) (ACS1) (Palmitoyl-CoA ligase 2);

(3077:) Long-chain-fatty-acid--CoA ligase 3 (Long-chain acyl-CoA synthetase3) (LACS 3); (3078:) Long-chain-fatty-acid--CoA ligase 4 (Long-chain acyl-CoA synthetase4) (LACS 4); (3079:) Long-chain-fatty-acid--CoA ligase 5 (Long-chain acyl-CoA synthetase5) (LACS 5); (3080:) Long-chain-fatty-acid--CoA ligase 6 (Long-chain acyl-CoA synthetase6) (LACS 6); (3081:) "Low affinity immunoglobulin epsilon Fc receptor (Lymphocyte IgEreceptor) (Fc-epsilon-RII) (BLAST-2) (Immunoglobulin E-bindingfactor) (CD23 antigen) [Contains:) Low affinity immunoglobulinepsilon Fc receptor membrane-bound form; Low affinityimmunoglobulin epsilon Fc receptor soluble form]."; (3082:) Low affinity immunoglobulin gamma Fc region receptor II-a precursor(Fc-gamma RII-a) (FcRII-a) (IgG Fc receptor II-a) (Fc-gamma-RIIa)(CD32 antigen) (CDw32); (3083:) Low affinity immunoglobulin gamma Fc region receptor II-b precursor(Fc-gamma RII-b) (FcRII-b) (IgG Fc receptor II-b) (Fc-gamma-RIIb)(CD32 antigen) (CDw32); (3084:) Low affinity immunoglobulin gamma Fc region receptor II-c precursor(Fc-gamma RII-c) (FcRII-c) (IgG Fc receptor II-c) (Fc-gamma-RIIc)(CD32 antigen) (CDw32); (3085:) Low affinity immunoglobulin gamma Fc region receptor III-Aprecursor (IgG Fc receptor III-2) (Fc-gamma RIII-alpha) (Fc-gammaRIIIa) (FcRIIIa) (Fc-gamma RIII) (FcRIII) (FcR-10) (CD16a antigen); (3086:) Low affinity immunoglobulin gamma Fc region receptor III-Bprecursor (IgG Fc receptor III-1) (Fc-gamma RIII-beta) (Fc-gammaRIIIb) (FcRIIIb) (Fc-gamma RIII) (FcRIII) (FcR-10) (CD16b antigen); (3087:) low density lipoprotein receptor precursor [Homo sapiens]; (3088:) low density lipoprotein-related protein 1 [Homo sapiens]; (3089:) Low molecular weight phosphotyrosine protein phosphatase (LMW-PTP)(Low molecular weight cytosolic acid phosphatase) (Red cell acidphosphatase 1) (PTPase) (Adipocyte acid phosphatase); (3090:) Low-density lipoprotein receptor precursor (LDL receptor); (3091:) Low-density lipoprotein receptor-related protein 1 precursor (LRP)(Alpha-2-macroglobulin receptor) (A2MR) (Apolipoprotein E receptor)(APOER) (CD91 antigen); (3092:) Low-density lipoprotein receptor-related protein 10 precursor; (3093:) Low-density lipoprotein receptor-related protein 11 precursor; (3094:) Low-density lipoprotein receptor-related protein 12 precursor(Suppressor of tumorigenicity protein 7); (3095:) Low-density lipoprotein receptor-related protein 1B precursor(Low-density lipoprotein receptor-related protein-deleted in tumor)(LRP-DIT); (3096:) Low-density lipoprotein receptor-related protein 2 precursor(Megalin) (Glycoprotein 330) (gp330); (3097:) Low-density lipoprotein receptor-related protein 3 precursor(hLRp105); (3098:) Low-density lipoprotein receptor-related protein 4 precursor(Multiple epidermal growth factor-like domains 7); (3099:) Low-density lipoprotein receptor-related protein 5

precursor; (3100:) Low-density lipoprotein receptor-related protein 6 precursor; (3101:) Low-density lipoprotein receptor-related protein 8 precursor(Apolipoprotein E receptor 2); (3102:) L-pipecolic acid oxidase [Homo sapiens]; (3103:) LRAP protein [Homo sapiens]; (3104:) L-serine dehydratase (L-serine deaminase); (3105:) L-UBC [Homo sapiens]; (3106:) luteinizing hormone/choriogonadotropin receptor precursor [Homosapiens]; (3107:) Lutheran blood group glycoprotein precursor (B-CAM cell surfaceglycoprotein) (Auberger B antigen) (F8/G253 antigen) (CD239antigen); (3108:) Lutropin-choriogonadotropic hormone receptor precursor (LH/CG-R)(LSH-R) (Luteinizing hormone receptor) (LHR); (3109:) L-xylulose reductase (XR) (Dicarbonyl/L-xylulose reductase) (Kidneydicarbonyl reductase) (kiDCR) (Carbonyl reductase II) (Spermsurface protein P34H); (3110:) Lymphatic vessel endothelial hyaluronic acid receptor 1 precursor(LYVE-1) (Cell surface retention sequence-binding protein 1)(CRSBP-1) (Hyaluronic acid receptor) (Extracellular linkdomain-containing protein 1); (3111:) Lymphocyte antigen 75 precursor (DEC-205) (gp200-MR6) (CD205antigen); (3112:) Lysine-specific histone demethylase 1 (Flavin-containing amineoxidase domain-containing protein 2) (BRAF35-HDAC complex proteinBHC110); (3113:) Lysophosphatidic acid receptor 4 (LPA receptor 4) (LPA-4) (P2Ypurinoceptor 9) (P2Y9) (Purinergic receptor 9) (G-protein coupledreceptor 23) (P2Y5-like receptor); (3114:) Lysophosphatidic acid receptor Edg-2 (LPA receptor 1) (LPA-1); (3115:) Lysophosphatidic acid receptor Edg-4 (LPA receptor 2) (LPA-2); (3116:) Lysophosphatidic acid receptor Edg-7 (LPA receptor 3) (LPA-3); (3117:) lysophospholipase 3 (lysosomal phospholipase A2) [Homo sapiens]; (3118:) "Lysosomal alpha-glucosidase precursor (Acid maltase) (Aglucosidasealfa) [Contains:) 76 kDa lysosomal alpha-glucosidase; 70 kDalysosomal alpha-glucosidase]."; (3119:) "Lysosomal alpha-mannosidase precursor (Mannosidase, alpha B)(Lysosomal acid alpha-mannosidase) (Laman) (Mannosidase alpha class2B member 1) [Contains:) Lysosomal alpha-mannosidase A peptide;Lysosomal alpha-mannosidase B peptide; Lysosomal alpha-mannosidaseC peptide; Lysosomal alpha-mannosidase D peptide; Lysosomalalpha-mannosidase E peptide]."; (3120:) lysosomal enzyme beta-N-acetylhexosaminidase A [Homo sapiens]; (3121:) lysosomal glucocerebrosidase precursor [Homo sapiens]; (3122:) lysosomal neuraminidase precursor [Homo sapiens]; (3123:) "Lysosomal protective protein precursor (Cathepsin A)(Carboxypeptidase C) (Protective protein for beta-galactosidase)[Contains:) Lysosomal protective protein 32 kDa chain; Lysosomalprotective protein 20 kDa chain]."; (3124:) Lysosomal thioesterase PPT2 precursor (PPT-2) (S-thioesterase G14); (3125:) Lysosome membrane protein 2

(Lysosome membrane protein II) (LIMPII) (Scavenger receptor class B member 2) (85 kDa lysosomalmembrane sialoglycoprotein) (LGP85) (CD36 antigen-like 2); (3126:) Lysozyme-like protein 4 precursor; (3127:) lysyl hydroxylase precursor [Homo sapiens]; (3128:) lysyl oxidase preproprotein [Homo sapiens]; (3129:) lysyl oxidase-like 2 precursor [Homo sapiens]; (3130:) lysyl oxidase-like 3 precursor [Homo sapiens]; (3131:) lysyl-tRNA synthetase [Homo sapiens]; (3132:) M2-type pyruvate kinase; (3133:) MACH-alpha-1 [Homo sapiens]; (3134:) MACH-alpha-2 [Homo sapiens]; (3135:) MACH-alpha-3 [Homo sapiens]; (3136:) MACH-beta-3 [Homo sapiens]; (3137:) MACH-beta-4 [Homo sapiens]; (3138:) Macrophage colony-stimulating factor 1 receptor precursor (CSF-1-R)(Fms proto-oncogene) (c-fms) (CD115 antigen); (3139:) Macrophage mannose receptor 1 precursor (MMR) (CD206 antigen); (3140:) Macrophage mannose receptor 2 precursor (Urokinasereceptor-associated protein) (Endocytic receptor 180) (CD280antigen); (3141:) Macrophage receptor MARCO (Macrophage receptor with collagenousstructure) (Scavenger receptor class A member 2); (3142:) Macrophage scavenger receptor types I and II (Macrophage acetylatedLDL receptor I and II) (Scavenger receptor class A member 1) (CD204antigen); (3143:) "Macrophage-stimulating protein receptor precursor (MSP receptor)(p185-Ron) (CD136 antigen) (CDw136) [Contains:Macrophage-stimulating protein receptor alpha chain;Macrophage-stimulating protein receptor beta chain]."; (3144:) Magnesium-dependent phosphatase 1 (MDP-1); (3145:) major histocompatibility complex, class II, DP alpha 1 precursor[Homo sapiens]; (3146:) major histocompatibility complex, class II, DQ alpha 2 [Homosapiens]; (3147:) malate dehydrogenase (oxaloacetate decarboxylating) (NADP+) [Homosapiens]; (3148:) male sterility domain containing 1 [Homo sapiens]; (3149:) male sterility domain containing 2 [Homo sapiens]; (3150:) Maleylacetoacetate isomerase (MAAI) (Glutathione S-transferase zeta1) (GSTZ1-1); (3151:) Malic enzyme 1, NADP(+)-dependent, cytosolic [Homo sapiens]; (3152:) malic enzyme 2 [Homo sapiens]; (3153:) malic enzyme 2, NAD(+)-dependent, mitochondrial [Homo sapiens]; (3154:) malic enzyme 3, NADP(+)-dependent, mitochondrial [Homo sapiens]; (3155:) Malonyl CoA-acyl carrier protein transacylase, mitochondrialprecursor (MCT) (Mitochondrial malonyltransferase); (3156:) maltase-glucoamylase [Homo sapiens]; (3157:) manganese superoxide dismutase isoform A precursor [Homo sapiens]; (3158:) manganese superoxide dismutase isoform B precursor [Homo sapiens]; (3159:) mannan-binding lectin serine protease 2 isoform 1 precursor [Homosapiens]; (3160:) mannan-binding lectin serine protease 2 isoform 2 precursor [Homosapiens]; (3161:) "Mannan-binding

lectin serine protease 2 precursor (Mannose-bindingprotein-associated serine protease 2) (MASP-2) (MBL-associatedserine protease 2) [Contains:) Mannan-binding lectin serine protease2 A chain; Mannan-binding lectin serine protease 2 B chain]."; (3162:) mannosidase, alpha, class 1A, member 1 [Homo sapiens]; (3163:) mannosidase, alpha, class 2A, member 1 [Homo sapiens]; (3164:) mannosidase, alpha, class 2B, member 1 precursor [Homo sapiens]; (3165:) mannosidase, alpha, class 2C, member 1 [Homo sapiens]; (3166:) mannosidase, endo-alpha [Homo sapiens]; (3167:) mannosyl (alpha-1,3-)-glycoproteinbeta-1,2-N-acetylglucosaminyltransferase [Homo sapiens]; (3168:) mannosyl (alpha-1,6-)-glycoproteinbeta-1,2-N-acetylglucosaminyltransferase [Homo sapiens]; (3169:) mannosyl (beta-1,4-)-glycoproteinbeta-1,4-N-acetylglucosaminyltransferase [Homo sapiens]; (3170:) Mannosyl-oligosaccharide 1,2-alpha-mannosidase IA (Processingalpha-1,2-mannosidase IA) (Alpha-1,2-mannosidase IA) (Mannosidasealpha class 1A member 1) (Man(9)-alpha-mannosidase)(Man9-mannosidase); (3171:) Mannosyl-oligosaccharide 1,2-alpha-mannosidase IB (Processingalpha-1,2-mannosidase IB) (Alpha-1,2-mannosidase IB) (Mannosidasealpha class 1A member 2); (3172:) Mannosyl-oligosaccharide 1,2-alpha-mannosidase IC (Processingalpha-1,2-mannosidase IC) (Alpha-1,2-mannosidase IC) (Mannosidasealpha class 1C member 1) (HMIC); (3173:) mannosyl-oligosaccharide glucosidase [Homo sapiens]; (3174:) MAP kinase-activated protein kinase 2 (MAPK-activated proteinkinase 2) (MAPKAP kinase 2) (MAPKAPK-2) (MK2); (3175:) MAP kinase-activated protein kinase 5 (MAPK-activated proteinkinase 5) (MAPKAP kinase 5) (p38-regulated/activated proteinkinase); (3176:) MAP kinase-interacting serine/threonine-protein kinase 1 (MAPkinase signal-integrating kinase 1) (Mnk1); (3177:) MAPK/MAK/MRK overlapping kinase (MOK protein kinase) (Renal tumorantigen 1) (RAGE-1); (3178:) marapsin [Homo sapiens]; (3179:) MAS proto-oncogene; (3180:) masA [Homo sapiens]; (3181:) Mas-related G-protein coupled receptor member D (Beta-alaninereceptor) (G-protein coupled receptor TGR7); (3182:) Mas-related G-protein coupled receptor member E (G-protein coupledreceptor 167); (3183:) Mas-related G-protein coupled receptor member F (Mas-related gene Fprotein) (G-protein coupled receptor 168); (3184:) Mas-related G-protein coupled receptor member G (G-protein coupledreceptor 169); (3185:) Mas-related G-protein coupled receptor member X1 (Sensoryneuron-specific G-protein coupled receptor 3/4); (3186:) Mas-related G-protein coupled receptor member X2; (3187:) Mas-related G-protein coupled receptor member X3 (Sensoryneuron-specific G-protein coupled receptor

1/2); (3188:) Mas-related G-protein coupled receptor member X4 (Sensoryneuron-specific G-protein coupled receptor 5/6); (3189:) Mas-related G-protein coupled receptor MRG (MAS-R) (MAS1-like); (3190:) mast cell function-associated antigen [Homo sapiens]; (3191:) Mast/stem cell growth factor receptor precursor (SCFR)(Proto-oncogene tyrosine-protein kinase Kit) (c-kit) (CD117antigen); (3192:) matrix metalloproteinase 1 preproprotein [Homo sapiens]; (3193:) matrix metalloproteinase 10 preproprotein [Homo sapiens]; (3194:) matrix metalloproteinase 11 preproprotein [Homo sapiens]; (3195:) matrix metalloproteinase 12 preproprotein [Homo sapiens]; (3196:) matrix metalloproteinase 13 preproprotein [Homo sapiens]; (3197:) matrix metalloproteinase 14 preproprotein [Homo sapiens]; (3198:) matrix metalloproteinase 15 preproprotein [Homo sapiens]; (3199:) matrix metalloproteinase 16 isoform 1 preproprotein [Homo sapiens]; (3200:) matrix metalloproteinase 16 isoform 2 preproprotein [Homo sapiens]; (3201:) matrix metalloproteinase 17 preproprotein [Homo sapiens]; (3202:) matrix metalloproteinase 19 isoform 2 precursor [Homo sapiens]; (3203:) matrix metalloproteinase 19 isoform rasi-1 preproprotein [Homosapiens]; (3204:) matrix metalloproteinase 2 preproprotein [Homo sapiens]; (3205:) matrix metalloproteinase 20 preproprotein [Homo sapiens]; (3206:) matrix metalloproteinase 23B precursor [Homo sapiens]; (3207:) matrix metalloproteinase 26 preproprotein [Homo sapiens]; (3208:) matrix metalloproteinase 28 isoform 1 preproprotein [Homo sapiens]; (3209:) matrix metalloproteinase 28 isoform 3 [Homo sapiens]; (3210:) matrix metalloproteinase 3 preproprotein [Homo sapiens]; (3211:) matrix metalloproteinase 7 preproprotein [Homo sapiens]; (3212:) matrix metalloproteinase 8 preproprotein [Homo sapiens]; (3213:) matrix metalloproteinase 9 preproprotein [Homo sapiens]; (3214:) Matrix metalloproteinase-16 precursor (MMP-16) (Membrane-typematrix metalloproteinase 3) (MT-MMP 3) (MTMMP3) (Membrane-type-3matrix metalloproteinase) (MT3-MMP) (MT3MMP) (MMP-X2); (3215:) Matrix metalloproteinase-19 precursor (MMP-19) (Matrixmetalloproteinase RASI) (MMP-18); (3216:) "Matrix metalloproteinase-9 precursor (MMP-9) (92 kDa type IVcollagenase) (92 kDa gelatinase) (Gelatinase B) (GELB) [Contains:67 kDa matrix metalloproteinase-9; 82 kDa matrixmetalloproteinase-9]."; (3217:) matrix, extracellular phosphoglycoprotein with ASARM motif (bone)[Homo sapiens]; (3218:) Mch3 isoform alpha; (3219:) Mch3 isoform beta; (3220:) "MDMCSF (EC 1.5.1.5; EC 3.5.4.9; EC 6.3.4.3)."; (3221:) MDS010 [Homo sapiens]; (3222:) ME2 protein [Homo sapiens]; (3223:) Mediator complex subunit 4 (Mediator of RNA polymerase

IItranscription subunit 4) (Vitamin D3 receptor-interacting proteincomplex 36 kDa component) (DRIP36) (Activator-recruited cofactor 36kDa component) (ARC36) (TRAP/SMCC/PC2 subunit p36 subunit); (3224:) Mediator of RNA polymerase II transcription subunit 12 (Thyroidhormone receptor-associated protein complex 230 kDa component)(Trap230) (Activator-recruited cofactor 240 kDa component) (ARC240)(CAG repeat protein 45) (OPA-containing protein) (Trinucleotiderepeat-containing gene 11 protein); (3225:) Mediator of RNA polymerase II transcription subunit 8 homolog(Activator-recruited cofactor 32 kDa component) (ARC32); (3226:) mediator of RNA polymerase II transcription subunit MED8 isoform 1[Homo sapiens]; (3227:) mediator of RNA polymerase II transcription subunit MED8 isoform 2[Homo sapiens]; (3228:) mediator of RNA polymerase II transcription subunit MED8 isoform 3[Homo sapiens]; (3229:) mediator of RNA polymerase II transcription subunit MED8 isoform 4[Homo sapiens]; (3230:) medium-chain acyl-CoA dehydrogenase (EC 1.3.99.3); (3231:) medium-chain acyl-CoA dehydrogenase; (3232:) Medium-chain specific acyl-CoA dehydrogenase, mitochondrialprecursor (MCAD); (3233:) Meis1 homolog [Homo sapiens]; (3234:) Melanin-concentrating hormone receptor 1 (MCH receptor 1) (MCHR-1)(MCH-R1) (MCH1R) (MCH-1R) (MCHR) (G-protein coupled receptor 24)(Somatostatin receptor-like protein) (SLC-1); (3235:) Melanin-concentrating hormone receptor 2 (MCH receptor 2) (MCHR-2)(MCH-R2) (MCH2R) (MCH-2R) (MCH2) (G-protein coupled receptor 145)(GPRv17); (3236:) Melanocortin receptor 3 (MC3-R); (3237:) Melanocortin receptor 4 (MC4-R); (3238:) Melanocortin receptor 5 (MC5-R) (MC-2); (3239:) Melanocyte protein Pmel 17 precursor (Melanocyte lineage-specificantigen GP100) (Melanoma-associated ME20 antigen) (ME20M/ME20S)(ME20-M/ME20-S) (95 kDa melanocyte-specific secreted glycoprotein); (3240:) Melanocyte-stimulating hormone receptor (MSH-R) (Melanotropinreceptor) (Melanocortin receptor 1) (MC1-R); (3241:) Melanopsin (Opsin-4); (3242:) Melatonin receptor type 1A (Mel-1A-R) (Mel1a melatonin receptor); (3243:) Melatonin receptor type 1B (Mel-1B-R) (Mel1b melatonin receptor); (3244:) Melatonin-related receptor (G protein-coupled receptor 50) (H9); (3245:) membrane alanine aminopeptidase precursor [Homo sapiens]; (3246:) membrane associated guanylate kinase, WW and PDZ domain containing2 [Homo sapiens]; (3247:) Membrane copper amine oxidase (Semicarbazide-sensitive amineoxidase) (SSAO) (Vascular adhesion protein 1) (VAP-1) (HPAO); (3248:) membrane metallo-endopeptidase [Homo sapiens]; (3249:) Membrane metallo-endopeptidase-like 1 (Membranemetallo-endopeptidase-like 2) (Neprilysin-2) (Neprilysin II) (NL2)(NEPII) (NEP2(m)) [Contains:) Membrane metallo-

endopeptidase-like 1,soluble form (Neprilysin-2 secreted) (NEP2(s))]; (3250:) Membrane progestin receptor alpha (mPR alpha) (Progestin and adipoQreceptor family member VII); (3251:) Membrane progestin receptor beta (mPR beta) (Progestin and adipoQreceptor family member VIII) (Lysosomal membrane protein inbrain-1); (3252:) Membrane progestin receptor gamma (mPR gamma) (Progestin and adipoQreceptor family member V); (3253:) Membrane-associated progesterone receptor component 1 (mPR); (3254:) Membrane-associated progesterone receptor component 2 (Progesteronemembrane-binding protein) (Steroid receptor protein DG6); (3255:) membrane-associated prostaglandin E synthase (EC 5.3.99.3) -2 - human; (3256:) Membrane-associated tyrosine- and threonine-specificcdc2-inhibitory kinase (Myt1 kinase); (3257:) Membrane-bound transcription factor site 1 protease precursor (S1Pendopeptidase) (Site-1 protease) (Subtilisin/kexin-isozyme 1)(SKI-1); (3258:) Membrane-spanning 4-domains subfamily A member 10; (3259:) Membrane-spanning 4-domains subfamily A member 12; (3260:) Membrane-spanning 4-domains subfamily A member 3(Hematopoietic-specific transmembrane 4 protein) (HTm4) (CD20antigen-like protein); (3261:) Membrane-spanning 4-domains subfamily A member 4A (Four-spantransmembrane protein 1) (CD20 antigen-like 1); (3262:) Membrane-spanning 4-domains subfamily A member 4E; (3263:) Membrane-spanning 4-domains subfamily A member 5 (Testis-expressedtransmembrane 4 protein) (CD20 antigen-like 2); (3264:) Membrane-spanning 4-domains subfamily A member 6A (Four-spantransmembrane protein 3) (CD20 antigen-like 3); (3265:) Membrane-spanning 4-domains subfamily A member 6E; (3266:) Membrane-spanning 4-domains subfamily A member 7(CD20/FC-epsilon-RI-beta family member 4) (Four-span transmembraneprotein 2) (CD20 antigen-like 4); (3267:) Membrane-spanning 4-domains subfamily A member 8B (Four-spantransmembrane protein 4); (3268:) membrane-type mosaic serine protease [Homo sapiens]; (3269:) menage a trois 1 (CAK assembly factor) [Homo sapiens]; (3270:) meningioma expressed antigen 5 (hyaluronidase) [Homo sapiens]; (3271:) meprin A, alpha (PABA peptide hydrolase) [Homo sapiens]; (3272:) meprin A, beta [Homo sapiens]; (3273:) mercaptopyruvate sulfurtransferase variant [Homo sapiens]; (3274:) mesotrypsin preproprotein [Homo sapiens]; (3275:) mesotrypsinogen [Homo sapiens]; (3276:) Metabotropic glutamate receptor 1 precursor (mGluR1); (3277:) Metabotropic glutamate receptor 2 precursor (mGluR2); (3278:) Metabotropic glutamate receptor 3 precursor (mGluR3); (3279:) Metabotropic glutamate receptor 4 precursor (mGluR4); (3280:) metabotropic glutamate receptor 5 A - human; (3281:) metabotropic glutamate receptor 5 B -

human; (3282:) Metabotropic glutamate receptor 5 precursor (mGluR5); (3283:) Metabotropic glutamate receptor 6 precursor (mGluR6); (3284:) Metabotropic glutamate receptor 7 precursor (mGluR7); (3285:) Metabotropic glutamate receptor 8 precursor (mGluR8); (3286:) metallopeptidase [Homo sapiens]; (3287:) metallothionein 1A [Homo sapiens]; (3288:) methionine sulfoxide reductase A [Homo sapiens]; (3289:) methionine synthase reductase isoform 1 [Homo sapiens]; (3290:) methionine synthase reductase isoform 2 [Homo sapiens]; (3291:) methionyl aminopeptidase 2 [Homo sapiens]; (3292:) Methionyl-tRNA synthetase, mitochondrial precursor(Methionine--tRNA ligase 2) (Mitochondrial methionine--tRNA ligase)(MtMetRS); (3293:) methyl sterol oxidase; (3294:) Methylated-DNA--protein-cysteine methyltransferase(6-O-methylguanine-DNA methyltransferase) (MGMT)(O-6-methylguanine-DNA-alkyltransferase); (3295:) Methylcrotonoyl-CoA carboxylase subunit alpha, mitochondrialprecursor (3-methylcrotonyl-CoA carboxylase 1) (MCCase subunitalpha) (3-methylcrotonyl-CoA:carbon dioxide ligase subunit alpha)(3-methylcrotonyl-CoA carboxylase biotin-containing subunit); (3296:) methylcrotonoyl-Coenzyme A carboxylase 1 (alpha) [Homo sapiens]; (3297:) methylcrotonoyl-Coenzyme A carboxylase 1 (alpha) variant [Homosapiens]; (3298:) methylcrotonoyl-Coenzyme A carboxylase 2 (beta) [Homo sapiens]; (3299:) methylene tetrahydrofolate dehydrogenase 2 isoform A precursor[Homo sapiens]; (3300:) methylene tetrahydrofolate dehydrogenase 2 isoform B [Homosapiens]; (3301:) methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 1-like[Homo sapiens]; (3302:) methylenetetrahydrofolate dehydrogenase 1 [Homo sapiens]; (3303:) methylenetetrahydrofolate reductase [Homo sapiens]; (3304:) methylenetetrahydrofolate reductase intermediate form [Homosapiens]; (3305:) methylenetetrahydrofolate reductase long isoform [Homo sapiens]; (3306:) methylenetetrahydrofolate reductase short isoform [Homo sapiens]; (3307:) Methylenetetrahydrofolate reductase; (3308:) methylmalonyl Coenzyme A mutase precursor [Homo sapiens]; (3309:) Methylmalonyl-CoA mutase, mitochondrial precursor (MCM)(Methylmalonyl-CoA isomerase); (3310:) methylthioadenosine phosphorylase [Homo sapiens]; (3311:) methyltransferase like 3 [Homo sapiens]; (3312:) Mevalonate kinase (MK); (3313:) mevalonate kinase [Homo sapiens]; (3314:) mevalonate pyrophosphate decarboxylase; (3315:) MGC42638 protein [Homo sapiens]; (3316:) microphthalmia-associated transcription factor isoform 1 [Homosapiens]; (3317:) microphthalmia-associated transcription factor isoform 2 [Homosapiens]; (3318:) microphthalmia-associated transcription factor isoform 3 [Homosapiens]; (3319:) microphthalmia-associated transcription factor isoform 4

[Homosapiens]; (3320:) microphthalmia-associated transcription factor isoform 5 [Homosapiens]; (3321:) microphthalmia-associated transcription factor isoform 6 [Homosapiens]; (3322:) Microsomal glutathione S-transferase 1 (Microsomal GST-1)(Microsomal GST-I); (3323:) microsomal glutathione S-transferase 2 [Homo sapiens]; (3324:) Microsomal glutathione S-transferase 3 (Microsomal GST-3)(Microsomal GST-III); (3325:) microsomal glutathione S-transferase 3 [Homo sapiens]; (3326:) microtubule-associated protein tau isoform 1 [Homo sapiens]; (3327:) microtubule-associated protein tau isoform 2 [Homo sapiens]; (3328:) microtubule-associated protein tau isoform 3 [Homo sapiens]; (3329:) microtubule-associated protein tau isoform 4 [Homo sapiens]; (3330:) microtubule-associated proteins 1A/1B light chain 3 [Homo sapiens]; (3331:) migration-inducing gene 10 protein [Homo sapiens]; (3332:) migration-inducing protein 4 [Homo sapiens]; (3333:) Mih1/TX isoform beta [Homo sapiens]; (3334:) Mih1/TX isoform delta [Homo sapiens]; (3335:) Mih1/TX isoform gamma [Homo sapiens]; (3336:) Mineralocorticoid receptor (MR); (3337:) minichromosome maintenance protein 4 [Homo sapiens]; (3338:) minichromosome maintenance protein 6 [Homo sapiens]; (3339:) minichromosome maintenance protein 7 isoform 1 [Homo sapiens]; (3340:) minichromosome maintenance protein 7 isoform 2 [Homo sapiens]; (3341:) mitochondrial aldehyde dehydrogenase 2 precursor [Homo sapiens]; (3342:) mitochondrial C1-tetrahydrofolate synthetase - human; (3343:) mitochondrial dihydrolipoamide succinyltransferase [Homo sapiens]; (3344:) mitochondrial DNA polymerase accessory subunit precursor [Homosapiens]; (3345:) mitochondrial glycine cleavage system H-protein precursor [Homosapiens]; (3346:) Mitochondrial import receptor subunit TOM22 homolog (Translocase ofouter membrane 22 kDa subunit homolog) (hTom22) (1C9-2); (3347:) Mitochondrial intermediate peptidase, mitochondrial precursor(MIP); (3348:) mitochondrial malate dehydrogenase precursor [Homo sapiens]; (3349:) mitochondrial MTO1-3 [Homo sapiens]; (3350:) mitochondrial NAD(P)+ -dependent malic enzyme; (3351:) mitochondrial NADP(+)-dependent malic enzyme 3 [Homo sapiens]; (3352:) mitochondrial phosphoenolpyruvate carboxykinase 2 isoform 1precursor [Homo sapiens]; (3353:) mitochondrial phosphoenolpyruvate carboxykinase 2 isoform 2precursor [Homo sapiens]; (3354:) mitochondrial short-chain enoyl-coenzyme A hydratase 1 precursor[Homo sapiens]; (3355:) mitochondrial topoisomerase I [Homo sapiens]; (3356:) Mitochondrial translation optimization 1 homolog (S. cerevisiae)[Homo sapiens]; (3357:) mitochondrial translation optimization 1 homolog isoform a [Homosapiens]; (3358:) mitochondrial translation optimization 1 homolog isoform b

[Homosapiens]; (3359:) mitochondrial trifunctional protein, alpha subunit precursor [Homosapiens]; (3360:) mitochondrial trifunctional protein, beta subunit precursor [Homosapiens]; (3361:) Mitogen-activated protein kinase 1 (Extracellular signal-regulatedkinase 2) (ERK-2) (Mitogen-activated protein kinase 2) (MAP kinase2) (MAPK 2) (p42-MAPK) (ERT1); (3362:) mitogen-activated protein kinase 1 [Homo sapiens]; (3363:) Mitogen-activated protein kinase 10 (Stress-activated proteinkinase JNK3) (c-Jun N-terminal kinase 3) (MAP kinase p49 3F12); (3364:) Mitogen-activated protein kinase 11 (Mitogen-activated proteinkinase p38 beta) (MAP kinase p38 beta) (p38b) (p38-2)(Stress-activated protein kinase 2); (3365:) Mitogen-activated protein kinase 12 (Extracellular signal-regulatedkinase 6) (ERK-6) (ERK5) (Stress-activated protein kinase 3)(Mitogen-activated protein kinase p38 gamma) (MAP kinase p38gamma); (3366:) Mitogen-activated protein kinase 13 (Stress-activated proteinkinase 4) (Mitogen-activated protein kinase p38 delta) (MAP kinasep38 delta); (3367:) Mitogen-activated protein kinase 14 (Mitogen-activated proteinkinase p38 alpha) (MAP kinase p38 alpha) (Cytokine suppressiveanti-inflammatory drug-binding protein) (CSAID-binding protein)(CSBP) (MAX-interacting protein 2) (MAP kinase MXI2) (SAPK2A); (3368:) Mitogen-activated protein kinase 15 (Extracellular signal-regulatedkinase 8); (3369:) Mitogen-activated protein kinase 3 (Extracellular signal-regulatedkinase 1) (ERK-1) (Insulin-stimulated MAP2 kinase) (MAP kinase 1)(MAPK 1) (p44-ERK1) (ERT2) (p44-MAPK) (Microtubule-associatedprotein 2 kinase); (3370:) mitogen-activated protein kinase 3 isoform 1 [Homo sapiens]; (3371:) mitogen-activated protein kinase 3 isoform 2 [Homo sapiens]; (3372:) Mitogen-activated protein kinase 7 (Extracellular signal-regulatedkinase 5) (ERK-5) (ERK4) (BMK1 kinase); (3373:) Mitogen-activated protein kinase 8 (Stress-activated protein kinaseJNK1) (c-Jun N-terminal kinase 1) (JNK-46); (3374:) mitogen-activated protein kinase 8 isoform JNK1 alpha1 [Homosapiens]; (3375:) mitogen-activated protein kinase 8 isoform JNK1 alpha2 [Homosapiens]; (3376:) mitogen-activated protein kinase 8 isoform JNK1 beta1 [Homosapiens]; (3377:) mitogen-activated protein kinase 8 isoform JNK1 beta2 [Homosapiens]; (3378:) Mitogen-activated protein kinase 9 (Stress-activated protein kinaseJNK2) (c-Jun N-terminal kinase 2) (JNK-55); (3379:) mitogen-activated protein kinase kinase 1 [Homo sapiens]; (3380:) Mitogen-activated protein kinase kinase kinase (Mixed lineagekinase 4); (3381:) Mitogen-activated protein kinase kinase kinase 1 (MAPK/ERK kinasekinase 1) (MEK kinase 1) (MEKK 1); (3382:) Mitogen-activated protein kinase kinase kinase 10 (Mixed lineagekinase 2) (Protein kinase MST); (3383:) Mitogen-activated protein kinase kinase kinase 11 (Mixed

lineagekinase 3) (Src-homology 3 domain-containing proline-rich kinase); (3384:) mitogen-activated protein kinase kinase kinase 12 [Homo sapiens]; (3385:) Mitogen-activated protein kinase kinase kinase 13 (Mixed lineagekinase) (MLK) (Leucine zipper-bearing kinase); (3386:) Mitogen-activated protein kinase kinase kinase 15 (MAPK/ERK kinasekinase 15) (MEK kinase 15) (MEKK 15); (3387:) Mitogen-activated protein kinase kinase kinase 2 (MAPK/ERK kinasekinase 2) (MEK kinase 2) (MEKK 2); (3388:) Mitogen-activated protein kinase kinase kinase 3 (MAPK/ERK kinasekinase 3) (MEK kinase 3) (MEKK 3); (3389:) Mitogen-activated protein kinase kinase kinase 4 (MAPK/ERK kinasekinase 4) (MEK kinase 4) (MEKK 4) (MAP three kinase 1); (3390:) Mitogen-activated protein kinase kinase kinase 5 (MAPK/ERK kinasekinase 5) (MEK kinase 5) (MEKK 5) (Apoptosis signal-regulatingkinase 1) (ASK-1); (3391:) mitogen-activated protein kinase kinase kinase 5 [Homo sapiens]; (3392:) Mitogen-activated protein kinase kinase kinase 6; (3393:) Mitogen-activated protein kinase kinase kinase 9 (Mixed lineagekinase 1); (3394:) Mitogen-activated protein kinase kinase kinase MLT (MLK-likemitogen-activated protein triple kinase) (Leucine zipper-andsterile alpha motif-containing kinase) (Sterile alpha motif-andleucine zipper-containing kinase AZK) (Mixed lineage kinase-relatedkinase) (MLK-related kinase) (MRK) (Cervical cancer suppressor gene4 protein); (3395:) mitogen-activated protein kinase-activated protein kinase 2 isoform1 [Homo sapiens]; (3396:) mitogen-activated protein kinase-activated protein kinase 2 isoform2 [Homo sapiens]; (3397:) Mitotic checkpoint serine/threonine-protein kinase BUB1 (hBUB1)(BUB1A); (3398:) mitotic kinase-like protein-1 [Homo sapiens]; (3399:) Mitotic Kinesin Eg5; (3400:) MLH1+ins1a isoform [Homo sapiens]; (3401:) MLH1-Ex6 isoform [Homo sapiens]; (3402:) MLH3 protein [Homo sapiens]; (3403:) MMS2 [Homo sapiens]; (3404:) MOCS1 [Homo sapiens]; (3405:) MOCS1 protein [Homo sapiens]; (3406:) MOCS1A enzyme [Homo sapiens]; (3407:) MOCS1A protein [Homo sapiens]; (3408:) Molybdenum cofactor biosynthesis protein 1 A (MOCS1A); (3409:) Molybdenum cofactor biosynthesis protein 1 B (MOCS1B) (Molybdenumcofactor synthesis-step 1 protein A-B) (Molybdenum cofactorbiosynthesis protein C); (3410:) molybdenum cofactor biosynthesis protein A [Homo sapiens]; (3411:) molybdenum cofactor synthesis-step 1 protein isoform 1 [Homosapiens]; (3412:) molybdenum cofactor synthesis-step 1 protein isoform 2 [Homosapiens]; (3413:) molybdenum cofactor synthesis-step 1 protein isoform 3 [Homosapiens]; (3414:) molybdenum cofactor synthesis-step 1 protein isoform 4 [Homosapiens]; (3415:) molybdopterin synthase large subunit MOCS2B [Homo sapiens]; (3416:) molybdopterin synthase small subunit MOCS2A [Homo sapiens];

(3417:) monoacylglycerol O-acyltransferase 3 [Homo sapiens]; (3418:) Monoamine Oxidase A (MAO-A); (3419:) monoamine oxidase A [Homo sapiens]; (3420:) Monoamine Oxidase B (MAO-B); (3421:) Monocyte Chemoattractant Protein 1 (MCP-1) Receptor; (3422:) Monocyte to macrophage differentiation factor 2 (Progestin andadipoQ receptor family member X); (3423:) Monocyte to macrophage differentiation protein (Progestin andadipoQ receptor family member XI); (3424:) MOP-4 [Homo sapiens]; (3425:) mosaic serine protease [Homo sapiens]; (3426:) Motilin Receptor; (3427:) Motilin receptor (G-protein coupled receptor 38); (3428:) M-phase inducer phosphatase 1 (Dual specificity phosphataseCdc25A); (3429:) M-phase inducer phosphatase 2 (Dual specificity phosphataseCdc25B); (3430:) MRIT-alpha-1 [Homo sapiens]; (3431:) mRNA (guanine-7-)methyltransferase [Homo sapiens]; (3432:) mRNA 5' cap guanine-N-7 methyltransferase [Homo sapiens]; (3433:) mRNA cap guanine-N7 methyltransferase (mRNA(guanine-N(7)-)-methyltransferase) (RG7MT1) (mRNA capmethyltransferase) (hcm1p) (hCMT1) (hMet); (3434:) "mRNA capping enzyme (HCE) (HCAP1) [Includes:) Polynucleotide5'-triphosphatase (mRNA 5'-triphosphatase) (TPase); mRNAguanylyltransferase (GTP--RNA guanylyltransferase) (GTase)]."; (3435:) mRNA capping enzyme [Homo sapiens]; (3436:) mRNA decapping enzyme [Homo sapiens]; (3437:) mRNA decapping enzyme 1A (Transcription factor SMIF)(Smad4-interacting transcriptional co-activator); (3438:) mRNA decapping enzyme 1B; (3439:) mRNA decapping enzyme 2 (hDpc) (Nucleoside diphosphate-linkedmoiety X motif 20) (Nudix motif 20); (3440:) mRNA decapping enzyme variant [Homo sapiens]; (3441:) mRNA-decapping enzyme [Homo sapiens]; (3442:) MSTP042 [Homo sapiens]; (3443:) MTO1 isoform 1 [Homo sapiens]; (3444:) MTO1 isoform 2 [Homo sapiens]; (3445:) MTO1 protein [Homo sapiens]; (3446:) MTO1 protein isoform III [Homo sapiens]; (3447:) MTO1 protein isoform IV [Homo sapiens]; (3448:) MTO1-like protein [Homo sapiens]; (3449:) mucin 1 isoform 1 precursor [Homo sapiens]; (3450:) mucin 1 isoform 2 precursor [Homo sapiens]; (3451:) mucin 1 isoform 3 precursor [Homo sapiens]; (3452:) mucin 1 isoform 5 precursor [Homo sapiens]; (3453:) mucin 1 isoform 6 precursor [Homo sapiens]; (3454:) mucin 1 isoform 7 precursor [Homo sapiens]; (3455:) mucin 1 isoform 8 precursor [Homo sapiens]; (3456:) Mucin-1 (MUC1) Glycoprotein; (3457:) mu-crystallin [Homo sapiens]; (3458:) Mu-crystallin homolog (NADP-regulated thyroid-hormone-bindingprotein); (3459:) Multidrug Resistance-Associated Protein 1 (MRP1); (3460:) Multidrug resistance-associated protein 7 (ATP-binding cassettesub-family C member 10); (3461:) multifunctional protein CAD [Homo sapiens]; (3462:) multiple

exostoses-like 2 [Homo sapiens]; (3463:) Mu-Opioid Receptor; (3464:) Muscarinic acetylcholine receptor M1; (3465:) Muscarinic acetylcholine receptor M2; (3466:) Muscarinic acetylcholine receptor M3; (3467:) Muscarinic acetylcholine receptor M4; (3468:) Muscarinic acetylcholine receptor M5; (3469:) Muscarinic M1 Receptor; (3470:) Muscarinic M2 Receptor; (3471:) Muscarinic M3 Receptor; (3472:) Muscarinic M4 Receptor; (3473:) muscle beta 1 intergrin cytoplasmic domain binding protein MIBP[Homo sapiens]; (3474:) muscle creatine kinase [Homo sapiens]; (3475:) Muscle, skeletal receptor tyrosine protein kinase precursor(Muscle-specific tyrosine protein kinase receptor) (Muscle-specifickinase receptor) (MuSK); (3476:) mutant arylamine N-acetyltransferase [Homo sapiens]; (3477:) mutant I beta-1,6-N-acetylglucosaminyltransferase C form [Homosapiens]; (3478:) mutL 3 homolog (E.coli) [Homo sapiens]; (3479:) MutL homolog 1, colon cancer, nonpolyposis type 2 (E. coli) [Homosapiens]; (3480:) MutL homolog 3 (E. coli) [Homo sapiens]; (3481:) mutL homolog 3 isoform 1 [Homo sapiens]; (3482:) mutL homolog 3 isoform 2 [Homo sapiens]; (3483:) MutL protein homolog 1 [Homo sapiens]; (3484:) MutL protein homolog 1 variant [Homo sapiens]; (3485:) mutS homolog 2 [Homo sapiens]; (3486:) mutS homolog 6 [Homo sapiens]; (3487:) mutY homolog isoform 1 [Homo sapiens]; (3488:) mutY homolog isoform 2 [Homo sapiens]; (3489:) mutY homolog isoform 3 [Homo sapiens]; (3490:) mutY homolog isoform 4 [Homo sapiens]; (3491:) Mu-type opioid receptor (MOR-1); (3492:) Mycobacterial Arabinosyltransferases; (3493:) Mycobacterial Fatty Acid Synthetase I (FAS-I); (3494:) Mycobacterial Translocase I; (3495:) Mycobacterium Tuberculosis Adenosine Triphosphate (ATP) Synthase; (3496:) Mycobacterium Tuberculosis Enoyl-Acyl Carrier Protein Reductase (InhA); (3497:) Mycobacterium Tuberculosis Isocitrate Lyase (Icl); (3498:) myelin basic protein isoform 1 [Homo sapiens]; (3499:) myelin basic protein isoform 2 [Homo sapiens]; (3500:) myelin basic protein isoform 3 [Homo sapiens]; (3501:) myelin basic protein isoform 4 [Homo sapiens]; (3502:) myelin basic protein isoform 5 [Homo sapiens]; (3503:) myelin basic protein isoform 6 [Homo sapiens]; (3504:) Myelin Basic Protein Stimulator; (3505:) Myeloblastin precursor (Leukocyte proteinase 3) (PR-3) (PR3) (AGP7)(Wegener autoantigen) (P29) (C-ANCA antigen) (Neutrophil proteinase4) (NP-4); (3506:) myelodysplastic syndromes relative [Homo sapiens]; (3507:) myeloperoxidase [Homo sapiens]; (3508:) myofibrillogenesis regulator 1 isoform 1 [Homo sapiens]; (3509:) myofibrillogenesis regulator 1 isoform 2 [Homo sapiens]; (3510:) myofibrillogenesis regulator 1 isoform 3 [Homo sapiens]; (3511:) myo-inositol oxygenase [Homo sapiens]; (3512:) myo-inositol-1(or 4)-monophosphatase [Homo sapiens]; (3513:)

Myosin heavy chain, cardiac muscle beta isoform (MyHC-beta); (3514:) myosin light chain kinase isoform 1 [Homo sapiens]; (3515:) myosin light chain kinase isoform 2 [Homo sapiens]; (3516:) myosin light chain kinase isoform 3A [Homo sapiens]; (3517:) myosin light chain kinase isoform 3B [Homo sapiens]; (3518:) Myosin light chain kinase, smooth muscle (MLCK) (Telokin)(Kinase-related protein) (KRP); (3519:) Myosin regulatory light chain 2, nonsarcomeric (Myosin RLC); (3520:) Myosin regulatory light chain 2, smooth muscle isoform (Myosin RLC)(Myosin regulatory light chain 9) (LC20); (3521:) Myostatin; (3522:) myotonic dystrophy protein kinase [Homo sapiens]; (3523:) Myotonin-protein kinase (Myotonic dystrophy protein kinase) (MDPK)(DM-kinase) (DMK) (DMPK) (MT-PK); (3524:) myristoyl CoA:protein N-myristoyltransferase [Homo sapiens]; (3525:) Myristoylated Alanine-Rich C-Kinase Substrate (MARCKS); (3526:) myristoylated alanine-rich protein kinase C substrate [Homosapiens]; (3527:) myristoyl-CoA:protein N-myristoyltransferase [Homo sapiens]; (3528:) Na+/K+ -ATPase alpha 1 subunit isoform a proprotein [Homo sapiens]; (3529:) Na+/K+ -ATPase alpha 1 subunit isoform b proprotein [Homo sapiens]; (3530:) Na+/K+ -ATPase alpha 2 subunit proprotein [Homo sapiens]; (3531:) Na+/K+ -ATPase alpha 3 subunit [Homo sapiens]; (3532:) Na+/K+ -ATPase alpha 4 subunit isoform 1 [Homo sapiens]; (3533:) Na+/K+ -ATPase alpha 4 subunit isoform 2 [Homo sapiens]; (3534:) Na+/K+ -ATPase beta 1 subunit isoform a [Homo sapiens]; (3535:) Na+/K+ -ATPase beta 1 subunit isoform b [Homo sapiens]; (3536:) Na+/K+ -ATPase beta 2 subunit [Homo sapiens]; (3537:) Na+/K+ -ATPase beta 3 subunit [Homo sapiens]; (3538:) N-acetylated-alpha-linked acidic dipeptidase 2(N-acetylated-alpha-linked acidic dipeptidase II) (NAALADase II); (3539:) N-acetylated-alpha-linked-acidic dipeptidase (NAALADase); (3540:) N-acetylgalactosamine 4-sulfate 6-O-sulfotransferase (GalNAc4S-6ST)(B-cell RAG-associated gene protein) (hBRAG); (3541:) N-acetylgalactosamine 6-sulfate sulfatase [Homo sapiens]; (3542:) N-acetylgalactosamine-6-sulfatase precursor [Homo sapiens]; (3543:) N-acetylgalactosaminyltransferase 7 (Protein-UDPacetylgalactosaminyltransferase 7) (UDP-GalNAc:polypeptideN-acetylgalactosaminyltransferase 7) (Polypeptide GalNActransferase 7) (GalNAc-T7) (pp-GaNTase 7); (3544:) N-Acetylglucosamine kinase [Homo sapiens]; (3545:) N-acetylglucosamine-1-phosphate transferase [Homo sapiens]; (3546:) N-acetylglucosamine-1-phosphodiester alpha-N-acetylglucosaminidaseprecursor (Phosphodiester alpha-GlcNAcase) (Mannose6-phosphate-uncovering enzyme); (3547:) N-acetylglucosamine-1-phosphodiester alpha-N-acetylglucosaminidaseprecursor [Homo sapiens]; (3548:) N-

acetylglucosamine-1-phosphotransferase subunit gamma precursor(GlcNAc-1-phosphotransferase subunit gamma)(UDP-N-acetylglucosamine-1-phosphotransferase, subunit gamma); (3549:) "N-acetylglucosamine-1-phosphotransferase subunits alpha/betaprecursor (GlcNAc-1-phosphotransferase alpha/beta subunits)(UDP-N-acetylglucosamine-1-phosphotransferase alpha/beta subunits)(Stealth protein GNPTAB) [Contains:N-acetylglucosamine-1-phosphotransferase subunit alpha;N-acetylglucosamine-1-phosphotransferase subunit beta]."; (3550:) N-acetylglucosamine-1-phosphotransferase, gamma subunit [Homosapiens]; (3551:) N-acetylglucosamine-6-O-sulfotransferase (GlcNAc6ST) [Homosapiens]; (3552:) N-acetylglutamate synthase [Homo sapiens]; (3553:) "N-acetylglutamate synthase, mitochondrial precursor (Amino-acidacetyltransferase) [Contains:) N-acetylglutamate synthase long form;N-acetylglutamate synthase short form; N-acetylglutamate synthaseconserved domain form]."; (3554:) N-acetyllactosaminide beta-1,3-N-acetylglucosaminyltransferase(Poly-N-acetyllactosamine extension enzyme)(I-beta-1,3-N-acetylglucosaminyltransferase) (iGnT)(UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 6); (3555:) N-acetyllactosaminide beta-1,6-N-acetylglucosaminyl-transferase(N-acetylglucosaminyltransferase) (I-branching enzyme) (IGNT); (3556:) N-acetyllactosaminide beta-1,6-N-acetylglucosaminyltransferase[Homo sapiens]; (3557:) N-acetylneuraminate pyruvate lyase [Homo sapiens]; (3558:) N-acetylneuraminic acid phosphate synthase [Homo sapiens]; (3559:) N-acetyltransferase 1 [Homo sapiens]; (3560:) N-acetyltransferase 2 [Homo sapiens]; (3561:) N-acetyltransferase ESCO1 (Establishment of cohesion 1 homolog 1)(ECO1 homolog 1) (ESO1 homolog 1) (Establishment factor-likeprotein 1) (EFO1p) (hEFO1) (CTF7 homolog 1); (3562:) N-acylaminoacyl-peptide hydrolase [Homo sapiens]; (3563:) N-acylethanolamine-hydrolyzing acid amidase precursor(N-acylsphingosine amidohydrolase-like) (ASAH-like protein) (Acidceramidase-like protein); (3564:) N-acylglucosamine 2-epimerase (GlcNAc 2-epimerase)(N-acetyl-D-glucosamine 2-epimerase) (AGE) (Renin-binding protein)(RnBP); (3565:) N-acylneuraminate cytidylyltransferase (CMP-N-acetylneuraminic acidsynthetase) (CMP-NeuNAc synthetase); (3566:) N-acylneuraminate-9-phosphatase (Neu5Ac-9-Pase) (Haloaciddehalogenase-like hydrolase domain-containing protein 4); (3567:) N-acylsphingosine amidohydrolase (acid ceramidase) 1 isoform b[Homo sapiens]; (3568:) N-acylsphingosine amidohydrolase (acid ceramidase) 1 preproproteinisoform a [Homo sapiens]; (3569:) N-acylsphingosine amidohydrolase 3 [Homo sapiens]; (3570:) N-acylsphingosine amidohydrolase-like protein isoform 1

precursor[Homo sapiens]; (3571:) N-acylsphingosine amidohydrolase-like protein isoform 2 precursor[Homo sapiens]; (3572:) NAD kinase (Poly(P)/ATP NAD kinase); (3573:) NAD(P) dependent steroid dehydrogenase-like [Homo sapiens]; (3574:) NAD(P)H dehydrogenase [quinone] 1 (Quinone reductase 1)(NAD(P)H:quinone oxidoreductase 1) (QR1) (DT-diaphorase) (DTD)(Azoreductase) (Phylloquinone reductase) (Menadione reductase); (3575:) NAD(P)H menadione oxidoreductase 1, dioxin-inducible isoform a[Homo sapiens]; (3576:) NAD(P)H menadione oxidoreductase 1, dioxin-inducible isoform b[Homo sapiens]; (3577:) NAD(P)H menadione oxidoreductase 1, dioxin-inducible isoform c[Homo sapiens]; (3578:) NAD+ ADP-ribosyltransferase; (3579:) NAD-dependent deacetylase sirtuin-1 (hSIRT1) (hSIR2) (SIR2-likeprotein 1); (3580:) NAD-dependent deacetylase sirtuin-2 (SIR2-like) (SIR2-like protein2); (3581:) NAD-dependent deacetylase sirtuin-3, mitochondrial precursor(SIR2-like protein 3) (hSIRT3); (3582:) NAD-dependent malic enzyme, mitochondrial precursor (NAD-ME) (Malicenzyme 2); (3583:) NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 10, 42kDaprecursor [Homo sapiens]; (3584:) NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4, 9kDa [Homosapiens]; (3585:) NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 5 [Homosapiens]; (3586:) NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 8, 19kDa [Homosapiens]; (3587:) NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 2, 8kDaprecursor [Homo sapiens]; (3588:) NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 3, 12kDa [Homosapiens]; (3589:) NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15kDa [Homosapiens]; (3590:) NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 16kDaprecursor [Homo sapiens]; (3591:) NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 6, 17kDa isoform1 [Homo sapiens]; (3592:) NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 6, 17kDa isoform2 [Homo sapiens]; (3593:) NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 7, 18kDa [Homosapiens]; (3594:) NADH dehydrogenase (ubiquinone) Fe-S protein 1, 75kDa precursor[Homo sapiens]; (3595:) NADH dehydrogenase (ubiquinone) Fe-S protein 3, 30kDa(NADH-coenzyme Q reductase) [Homo sapiens]; (3596:) NADH dehydrogenase (ubiquinone) Fe-S protein 4, 18kDa(NADH-coenzyme Q reductase) [Homo sapiens]; (3597:) NADH dehydrogenase (ubiquinone) Fe-S protein 6, 13kDa(NADH-coenzyme Q reductase) [Homo sapiens]; (3598:) NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 1(NADH-ubiquinone oxidoreductase MWFE subunit) (Complex I-MWFE)(CI-MWFE); (3599:) NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 10,mitochondrial precursor (NADH-

ubiquinone oxidoreductase 42 kDasubunit) (Complex I-42kD) (CI-42kD); (3600:) NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 11(NADH-ubiquinone oxidoreductase subunit B14.7) (Complex I-B14.7)(CI-B14.7); (3601:) NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 12(NADH-ubiquinone oxidoreductase subunit B17.2) (Complex I-B17.2)(CI-B17.2) (CIB17.2) (13 kDa differentiation-associated protein); (3602:) NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 13(NADH-ubiquinone oxidoreductase B16.6 subunit) (Complex I-B16.6)(CI-B16.6) (Gene associated with retinoic-interferon-inducedmortality 19 protein) (GRIM-19) (Cell death-regulatory proteinGRIM-19); (3603:) NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 2(NADH-ubiquinone oxidoreductase B8 subunit) (Complex I-B8) (CI-B8); (3604:) NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 3(NADH-ubiquinone oxidoreductase B9 subunit) (Complex I-B9) (CI-B9); (3605:) NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 4(NADH-ubiquinone oxidoreductase MLRQ subunit) (Complex I-MLRQ)(CI-MLRQ); (3606:) NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 5(NADH-ubiquinone oxidoreductase 13 kDa-B subunit) (ComplexI-13kD-B) (CI-13kD-B) (Complex I subunit B13); (3607:) NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 6(NADH-ubiquinone oxidoreductase B14 subunit) (Complex I-B14)(CI-B14); (3608:) NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 7(NADH-ubiquinone oxidoreductase subunit B14.5a) (Complex I-B14.5a)(CI-B14.5a); (3609:) NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 8(NADH-ubiquinone oxidoreductase 19 kDa subunit) (Complex I-19kD)(CI-19kD) (Complex I-PGIV) (CI-PGIV); (3610:) NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 9,mitochondrial precursor (NADH-ubiquinone oxidoreductase 39 kDasubunit) (Complex I-39kD) (CI-39kD); (3611:) NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 1(NADH-ubiquinone oxidoreductase MNLL subunit) (Complex I-MNLL)(CI-MNLL); (3612:) NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 10(NADH-ubiquinone oxidoreductase PDSW subunit) (Complex I-PDSW)(CI-PDSW); (3613:) NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 11,mitochondrial precursor (NADH-ubiquinone oxidoreductase ESSSsubunit) (Complex I-ESSS) (CI-ESSS) (Neuronal protein 17.3) (p17.3)(Np17.3); (3614:) NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 2,mitochondrial precursor (NADH-ubiquinone oxidoreductase AGGGsubunit) (Complex I-AGGG) (CI-AGGG); (3615:) NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 3(NADH-ubiquinone oxidoreductase B12 subunit) (Complex I-

B12)(CI-B12); (3616:) NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 4(NADH-ubiquinone oxidoreductase B15 subunit) (Complex I-B15)(CI-B15); (3617:) NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 5,mitochondrial precursor (NADH-ubiquinone oxidoreductase SGDHsubunit) (Complex I-SGDH) (CI-SGDH); (3618:) NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 6(NADH-ubiquinone oxidoreductase B17 subunit) (Complex I-B17)(CI-B17); (3619:) NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 7(NADH-ubiquinone oxidoreductase B18 subunit) (Complex I-B18)(CI-B18) (Cell adhesion protein SQM1); (3620:) NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 8,mitochondrial precursor (NADH-ubiquinone oxidoreductase ASHIsubunit) (Complex I-ASHI) (CI-ASHI); (3621:) NADH dehydrogenase [ubiquinone] 1 beta subcomplex subunit 9(NADH-ubiquinone oxidoreductase B22 subunit) (Complex I-B22)(CI-B22); (3622:) NADH dehydrogenase [ubiquinone] 1 subunit C1, mitochondrialprecursor (NADH-ubiquinone oxidoreductase KFYI subunit) (ComplexI-KFYI) (CI-KFYI); (3623:) NADH dehydrogenase [ubiquinone] 1 subunit C2 (NADH-ubiquinoneoxidoreductase subunit B14.5b) (Complex I-B14.5b) (CI-B14.5b); (3624:) NADH dehydrogenase [ubiquinone] flavoprotein 1, mitochondrialprecursor (NADH-ubiquinone oxidoreductase 51 kDa subunit) (ComplexI-51kD) (CI-51kD) (NADH dehydrogenase flavoprotein 1); (3625:) NADH dehydrogenase [ubiquinone] flavoprotein 2, mitochondrialprecursor (NADH-ubiquinone oxidoreductase 24 kDa subunit); (3626:) NADH dehydrogenase [ubiquinone] flavoprotein 3, mitochondrialprecursor (NADH-ubiquinone oxidoreductase 9 kDa subunit) (ComplexI-9kD) (CI-9kD) (NY-REN-4 antigen); (3627:) NADH dehydrogenase [ubiquinone] iron-sulfur protein 2,mitochondrial precursor (NADH-ubiquinone oxidoreductase 49 kDasubunit) (Complex I-49kD) (CI-49kD); (3628:) NADH dehydrogenase [ubiquinone] iron-sulfur protein 3,mitochondrial precursor (NADH-ubiquinone oxidoreductase 30 kDasubunit) (Complex I-30kD) (CI-30kD); (3629:) NADH dehydrogenase [ubiquinone] iron-sulfur protein 4,mitochondrial precursor (NADH-ubiquinone oxidoreductase 18 kDasubunit) (Complex I-18 kDa) (CI-18 kDa) (Complex I-AQDQ) (CI-AQDQ); (3630:) NADH dehydrogenase [ubiquinone] iron-sulfur protein 5(NADH-ubiquinone oxidoreductase 15 kDa subunit) (Complex I-15 kDa)(CI-15 kDa); (3631:) NADH dehydrogenase [ubiquinone] iron-sulfur protein 6,mitochondrial precursor (NADH-ubiquinone oxidoreductase 13 kDa-Asubunit) (Complex I-13kD-A) (CI-13kD-A); (3632:) NADH dehydrogenase [ubiquinone] iron-sulfur protein 7,mitochondrial precursor (NADH-ubiquinone oxidoreductase 20 kDasubunit) (Complex I-20kD) (CI-20kD) (PSST

subunit); (3633:) "NADH-cytochrome b5 reductase (B5R) (Diaphorase-1) (Cytochrome b5reductase 3) [Contains:) NADH-cytochrome b5 reductase membrane-boundform; NADH-cytochrome b5 reductase soluble form]."; (3634:) NADH-cytochrome b5 reductase [Homo sapiens]; (3635:) "NADH-cytochrome b5 reductase; b5R [Homo sapiens]."; (3636:) NADH-ubiquinone oxidoreductase 75 kDa subunit, mitochondrialprecursor (Complex I-75kD) (CI-75kD); (3637:) NADP(+)-dependent malic enzyme - human (fragments); (3638:) "NADP+-dependent malic enzyme; malate dehydrogenase (oxaloacetatedecarboxylating) (NADP+) [Homo sapiens]."; (3639:) NADP-dependent isocitrate dehydrogenase [Homo sapiens]; (3640:) NADP-dependent malic enzyme (NADP-ME) (Malic enzyme 1); (3641:) NADP-dependent malic enzyme, mitochondrial precursor (NADP-ME)(Malic enzyme 3); (3642:) NADP-dependent malic enzyme; (3643:) NADPH oxidase 1 isoform long [Homo sapiens]; (3644:) NADPH oxidase 1 isoform long variant [Homo sapiens]; (3645:) NADPH oxidase 1 isoform short [Homo sapiens]; (3646:) NADPH oxidase 3 (gp91phox homolog 3) (GP91-3) (Mitogenic oxidase2); (3647:) NADPH oxidase 3 [Homo sapiens]; (3648:) NADPH oxidase 4 (Kidney superoxide-producing NADPH oxidase) (KOX-1)(Renal NAD(P)H-oxidase); (3649:) NADPH oxidase 5; (3650:) NADPH oxidase homolog 1 (NOX-1) (NOH-1) (NADH/NADPH mitogenicoxidase subunit P65-MOX) (Mitogenic oxidase 1) (MOX1); (3651:) NADPH oxidase, EF hand calcium-binding domain 5 [Homo sapiens]; (3652:) NADPH--cytochrome P450 reductase (CPR) (P450R); (3653:) nardilysin (N-arginine dibasic convertase) [Homo sapiens]; (3654:) Nardilysin precursor (N-arginine dibasic convertase) (NRDconvertase) (NRD-C); (3655:) N-arginine dibasic convertase [Homo sapiens]; (3656:) natriuretic peptide precursor A [Homo sapiens]; (3657:) natriuretic peptide precursor B preproprotein [Homo sapiens]; (3658:) Natriuretic Peptide Receptor A (NPR-A); (3659:) natriuretic peptide receptor A/guanylate cyclase A(atrionatriuretic peptide receptor A) [Homo sapiens]; (3660:) natriuretic peptide receptor B precursor [Homo sapiens]; (3661:) Natural cytotoxicity triggering receptor 1 precursor (Naturalkiller cell p46-related protein) (NKp46) (hNKp46) (NK-p46) (NKcell-activating receptor) (Lymphocyte antigen 94 homolog) (CD335antigen); (3662:) Natural cytotoxicity triggering receptor 2 precursor (Naturalkiller cell p44-related protein) (NKp44) (NK-p44) (NKcell-activating receptor) (Lymphocyte antigen 95 homolog) (CD336antigen); (3663:) Natural cytotoxicity triggering receptor 3 precursor (Naturalkiller cell p30-related protein) (NKp30) (NK-p30) (CD337 antigen); (3664:) Natural killer cell receptor 2B4 precursor (NKR2B4) (NK cell type Ireceptor protein 2B4) (h2B4) (CD244 antigen) (NK cellactivation-inducing ligand) (NAIL); (3665:)

Natural killer cells antigen CD94 (NK cell receptor) (Killer celllectin-like receptor subfamily D member 1) (KP43); (3666:) N-Cadherin; (3667:) NCUBE1 [Homo sapiens]; (3668:) N-deacetylase/N-sulfotransferase (heparan glucosaminyl) 2 [Homosapiens]; (3669:) NDUFS1 protein [Homo sapiens]; (3670:) NEDD4-like E3 ubiquitin-protein ligase WWP1 (WW domain-containingprotein 1) (Atropin-1-interacting protein 5) (AIP5); (3671:) NEDD4-like E3 ubiquitin-protein ligase WWP2 (WW domain-containingprotein 2) (Atrophin-1-interacting protein 2) (AIP2); (3672:) NEDD8 precursor (Ubiquitin-like protein Nedd8) (Neddylin); (3673:) NEDD8-activating enzyme E1 catalytic subunit (Ubiquitin-activatingenzyme 3) (NEDD8-activating enzyme E1C) (Ubiquitin-activatingenzyme E1C); (3674:) NEDD8-activating enzyme E1 regulatory subunit (Amyloidprotein-binding protein 1) (Amyloid beta precursor protein-bindingprotein 1, 59 kDa) (APP-BP1) (Protooncogene protein 1) (HPP1); (3675:) Nedd8-activating enzyme hUba3 [Homo sapiens]; (3676:) NEDD8-conjugating enzyme [Homo sapiens]; (3677:) Nedd8-conjugating enzyme hUbc12 [Homo sapiens]; (3678:) NEDD8-conjugating enzyme NCE2 [Homo sapiens]; (3679:) NEDD8-conjugating enzyme Ubc12 (Ubiquitin-conjugating enzyme E2 M)(NEDD8 protein ligase) (NEDD8 carrier protein); (3680:) Nef associated protein 1 [Homo sapiens]; (3681:) nei endonuclease VIII-like 1 [Homo sapiens]; (3682:) nei-like 2 [Homo sapiens]; (3683:) Nematode Nicotinic Acetylcholine Receptor (nAChR); (3684:) neo-poly(A) polymerase [Homo sapiens]; (3685:) nephrin [Homo sapiens]; (3686:) Nerve Growth Factor (NGF); (3687:) Netrin receptor DCC precursor (Tumor suppressor protein DCC)(Colorectal cancer suppressor); (3688:) Netrin receptor UNC5A precursor (Unc-5 homolog A) (Unc-5 homolog1); (3689:) Netrin receptor UNC5B precursor (Unc-5 homolog B) (Unc-5 homolog 2)(p53-regulated receptor for death and life protein 1); (3690:) Netrin receptor UNC5C precursor (Unc-5 homolog C) (Unc-5 homolog3); (3691:) Netrin receptor UNC5D precursor (Unc-5 homolog D) (Unc-5 homolog4); (3692:) neural stem cell-derived dendrite regulator [Homo sapiens]; (3693:) Neural Thread Protein (NTP); (3694:) Neuralized-like protein 2; (3695:) Neuraminidase; (3696:) neuraminidase precursor [Homo sapiens]; (3697:) neuroblastoma apoptosis-related protease [Homo sapiens]; (3698:) Neuroendocrine convertase 1 precursor (NEC 1) (PC1) (Prohormoneconvertase 1) (Proprotein convertase 1); (3699:) Neuroendocrine convertase 2 precursor (NEC 2) (PC2) (Prohormoneconvertase 2) (Proprotein convertase 2) (KEX2-like endoprotease 2); (3700:) Neurofibromin (Neurofibromatosis-related protein NF-1) [Contains:Neurofibromin truncated]; (3701:) neurofibromin isoform 1 [Homo sapiens]; (3702:) neurofibromin isoform 2

[Homo sapiens]; (3703:) neurofilament, light polypeptide 68kDa [Homo sapiens]; (3704:) "Neurogenic locus notch homolog protein 1 precursor (Notch 1) (hN1)(Translocation-associated notch protein TAN-1) [Contains:) Notch 1extracellular truncation; Notch 1 intracellular domain]."; (3705:) "Neurogenic locus notch homolog protein 2 precursor (Notch 2) (hN2)[Contains:) Notch 2 extracellular truncation; Notch 2 intracellulardomain]."; (3706:) "Neurogenic locus notch homolog protein 3 precursor (Notch 3)[Contains:) Notch 3 extracellular truncation; Notch 3 intracellulardomain]."; (3707:) "Neurogenic locus notch homolog protein 4 precursor (Notch 4)(hNotch4) [Contains:) Notch 4 extracellular truncation; Notch 4intracellular domain]."; (3708:) Neurokinin NK1 Receptor; (3709:) Neurokinin NK2 Receptor; (3710:) Neurokinin NK3 Receptor; (3711:) Neuromedin K receptor (NKR) (Neurokinin B receptor) (NK-3 receptor)(NK-3R) (Tachykinin receptor 3); (3712:) Neuromedin U receptor 1 (NMU-R1) (G-protein coupled receptor 66)(G-protein coupled receptor FM-3); (3713:) Neuromedin U receptor 2 (NMU-R2) (G-protein coupled receptor TGR-1)(G-protein coupled receptor FM-4); (3714:) Neuromedin-B receptor (NMB-R) (Neuromedin-B-preferring bombesinreceptor); (3715:) Neuronal acetylcholine receptor protein subunit alpha-10 precursor(Nicotinic acetylcholine receptor subunit alpha 10) (NACHR alpha10); (3716:) Neuronal acetylcholine receptor protein subunit alpha-3 precursor; (3717:) Neuronal acetylcholine receptor protein subunit alpha-5 precursor; (3718:) Neuronal acetylcholine receptor protein subunit alpha-6 precursor; (3719:) Neuronal acetylcholine receptor protein subunit alpha-9 precursor(Nicotinic acetylcholine receptor subunit alpha 9) (NACHR alpha 9); (3720:) Neuronal Nicotinic Acetylcholine Receptor (nAChR); (3721:) Neuronal pentraxin receptor; (3722:) neuronal tryptophan hydroxylase [Homo sapiens]; (3723:) neuron-derived receptor NOR-1 - human; (3724:) Neuropeptide FF receptor 1 (G-protein coupled receptor 147)(RFamide-related peptide receptor OT7T022); (3725:) Neuropeptide FF receptor 2 (Neuropeptide G-protein coupledreceptor) (G-protein coupled receptor 74) (G-protein coupledreceptor HLWAR77); (3726:) Neuropeptide S receptor (G-protein coupled receptor 154) (G-proteincoupled receptor for asthma susceptibility) (G-protein coupledreceptor PGR14); (3727:) Neuropeptide Y receptor type 1 (NPY1-R); (3728:) Neuropeptide Y receptor type 2 (NPY2-R) (NPY-Y2 receptor); (3729:) Neuropeptide Y receptor type 4 (NPY4-R) (Pancreatic polypeptidereceptor 1) (PP1); (3730:) Neuropeptide Y receptor type 5 (NPY5-R) (NPY-Y5 receptor) (Y5receptor) (NPYY5); (3731:) Neuropeptide Y Y1 Receptor (NPY Y1R); (3732:) Neuropeptide Y Y2 Receptor (NPY Y2R); (3733:) Neuropeptide Y Y4 Receptor (NPY Y4R); (3734:) Neuropeptide Y Y5 Receptor

(NPY Y5R); (3735:) Neuropeptides B/W receptor type 1 (G-protein coupled receptor 7); (3736:) Neuropeptides B/W receptor type 2 (G-protein coupled receptor 8); (3737:) Neuropilin and tolloid-like protein 1 precursor (Brain-specifictransmembrane protein containing 2 CUB and 1 LDL-receptor class Adomains protein 1); (3738:) Neuropilin and tolloid-like protein 2 precursor (Brain-specifictransmembrane protein containing 2 CUB and 1 LDL-receptor class Adomains protein 2); (3739:) Neuropilin-1 precursor (Vascular endothelial cell growth factor 165receptor) (CD304 antigen); (3740:) Neuropilin-2 precursor (Vascular endothelial cell growth factor 165receptor 2); (3741:) Neurotensin Receptor; (3742:) Neurotensin receptor type 1 (NT-R-1) (High-affinitylevocabastine-insensitive neurotensin receptor) (NTRH); (3743:) Neurotensin receptor type 2 (NT-R-2) (Levocabastine-sensitiveneurotensin receptor) (NTR2 receptor); (3744:) neurotensin/neuromedin N preproprotein [Homo sapiens]; (3745:) Neurotrophic factor production accelerator; (3746:) Neurotrophic Tyrosine Kinase Receptor 1 (NTRK1); (3747:) Neurotrophic Tyrosine Kinase Receptor 2 (NTRK2); (3748:) neurotrophin 5 preproprotein [Homo sapiens]; (3749:) neurotrypsin precursor [Homo sapiens]; (3750:) Neutral alpha-glucosidase AB precursor (Glucosidase II subunitalpha); (3751:) Neutral amino acid transporter B(0) (ATB(0)) (Sodium-dependentneutral amino acid transporter type 2) (RD114/simian type Dretrovirus receptor) (Baboon M7 virus receptor); (3752:) Neutral ceramidase (NCDase) (N-CDase) (Acylsphingosine deacylase 2)(N-acylsphingosine amidohydrolase 2) (BCDase) (LCDase) (hCD)[Contains:) Neutral ceramidase soluble form]; (3753:) Neutral Endopeptidase (NEP); (3754:) Neutral Sphingomyelinase (nSMase); (3755:) Neutrophil Cathepsin G; (3756:) Neutrophil collagenase precursor (Matrix metalloproteinase-8)(MMP-8) (PMNL collagenase) (PMNL-CL); (3757:) Neutrophil cytosol factor 4 (NCF-4) (Neutrophil NADPH oxidasefactor 4) (p40-phox) (p40phox); (3758:) neutrophil cytosolic factor 1 [Homo sapiens]; (3759:) neutrophil cytosolic factor 4 (40kD) isoform 1 [Homo sapiens]; (3760:) neutrophil cytosolic factor 4 (40kD) isoform 2 [Homo sapiens]; (3761:) Neutrophil Elastase; (3762:) NFS1 nitrogen fixation 1 [Homo sapiens]; (3763:) "N-glycosylase/DNA lyase [Includes:) 8-oxoguanine DNA glycosylase ;DNA-(apurinic or apyrimidinic site) lyase (AP lyase)]."; (3764:) Niacin Receptor; (3765:) Nicastrin precursor; (3766:) NICE-5 protein [Homo sapiens]; (3767:) Nicotinamide Adenine Dinucleotide synthetase (NADs); (3768:) nicotinamide mononucleotide adenylyl transferase [Homo sapiens]; (3769:) Nicotinamide mononucleotide adenylyltransferase 1 (NMNadenylyltransferase 1); (3770:) nicotinamide mononucleotide adenylyltransferase 2 isoform 1 [Homosapiens]; (3771:)

nicotinamide mononucleotide adenylyltransferase 2 isoform 2 [Homosapiens]; (3772:) nicotinamide nucleotide adenylyltransferase 1 [Homo sapiens]; (3773:) nicotinamide nucleotide adenylyltransferase 3 [Homo sapiens]; (3774:) nicotinamide riboside kinase 1 [Homo sapiens]; (3775:) Nicotinamide riboside kinase 2 (Integrin beta-1-binding protein 3)(Muscle integrin-binding protein) (MIBP); (3776:) nicotinamide riboside kinase 2 [Homo sapiens]; (3777:) Nicotinic acid receptor 1 (G-protein coupled receptor 109A)(G-protein coupled receptor HM74A); (3778:) Nicotinic acid receptor 2 (G-protein coupled receptor 109B)(G-protein coupled receptor HM74) (G-protein coupled receptorHM74B); (3779:) Nicotinic Receptor; (3780:) NifU-like N-terminal domain-containing protein, mitochondrialprecursor (NifU-like protein) (Iron-sulfur cluster assembly enzymeISCU); (3781:) Nitric Oxide Neutralizer; (3782:) Nitric Oxide Synthase (NOS); (3783:) nitric oxide synthase 1 (neuronal) [Homo sapiens]; (3784:) nitric oxide synthase 2A isoform 1 [Homo sapiens]; (3785:) nitric oxide synthase 2A isoform 2 [Homo sapiens]; (3786:) nitric oxide synthase 3 (endothelial cell) [Homo sapiens]; (3787:) nitric oxide synthase trafficking isoform 1 [Homo sapiens]; (3788:) nitric oxide synthase trafficking isoform 2 [Homo sapiens]; (3789:) Nitric oxide synthase, inducible (NOS type II) (Inducible NOsynthase) (Inducible NOS) (iNOS) (Hepatocyte NOS) (HEP-NOS); (3790:) nitric oxide synthase; (3791:) Nitric-oxide synthase IIC (NOS type II C) (NOSIIc); (3792:) Nitric-oxide synthase, brain (NOS type I) (Neuronal NOS) (N-NOS)(nNOS) (Constitutive NOS) (NC-NOS) (bNOS); (3793:) Nitric-oxide synthase, endothelial (EC-NOS) (NOS type III) (NOSIII)(Endothelial NOS) (eNOS) (Constitutive NOS) (cNOS); (3794:) NKG2-A/NKG2-B type II integral membrane protein(NKG2-A/B-activating NK receptor) (NK cell receptor A) (CD159aantigen); (3795:) NKG2-C type II integral membrane protein (NKG2-C-activating NKreceptor) (NK cell receptor C) (CD159c antigen); (3796:) NKG2-D type II integral membrane protein (NKG2-D-activating NKreceptor) (NK cell receptor D) (Killer cell lectin-like receptorsubfamily K member 1) (CD314 antigen); (3797:) NKG2-E type II integral membrane protein (NKG2-E-activating NKreceptor) (NK cell receptor E); (3798:) NKG2-F type II integral membrane protein (NKG2-F-activating NKreceptor) (NK cell receptor F); (3799:) N-kinase; (3800:) NME1-NME2 protein [Homo sapiens]; (3801:) N-methyl purine DNA-glycosylase [Homo sapiens]; (3802:) N-Methyl-D-Aspartate (NMDA) Receptor; (3803:) N-methylpurine-DNA glycosylase isoform a [Homo sapiens]; (3804:) N-methylpurine-DNA glycosylase isoform b [Homo sapiens]; (3805:) N-methylpurine-DNA glycosylase isoform c [Homo sapiens]; (3806:) N-myristoyltransferase 1 [Homo sapiens]; (3807:) Nociceptin receptor (Orphanin FQ

receptor) (Kappa-type 3 opioidreceptor) (KOR-3); (3808:) NOD2 (CARD15) Receptor; (3809:) Non-Canonical UBiquitin Conjugating Enzyme 1 (NCUBE1) [Homosapiens]; (3810:) nonfunctional alpha(1,2)-fucosyltransferase [Homo sapiens]; (3811:) non-metastatic cells 1, protein (NM23A) expressed in isoform a[Homo sapiens]; (3812:) non-metastatic cells 1, protein (NM23A) expressed in isoform b[Homo sapiens]; (3813:) non-metastatic cells 2, protein (NM23B) expressed in [Homosapiens]; (3814:) Norepinephrine Reuptake; (3815:) Notch-1 Protein; (3816:) nov precursor [Homo sapiens]; (3817:) novel AMP-binding enzyme [Homo sapiens]; (3818:) novel protein [Homo sapiens]; (3819:) N-sulfoglucosamine sulfohydrolase (sulfamidase) [Homo sapiens]; (3820:) N-sulphoglucosamine sulphohydrolase [Homo sapiens]; (3821:) N-sulphoglucosamine sulphohydrolase precursor (Sulfoglucosaminesulfamidase) (Sulphamidase); (3822:) NT-3 growth factor receptor precursor (Neurotrophic tyrosine kinasereceptor type 3) (TrkC tyrosine kinase) (GP145-TrkC) (Trk-C); (3823:) N-terminal Asn amidase [Homo sapiens]; (3824:) nth endonuclease III-like 1 [Homo sapiens]; (3825:) N-Type Calcium Channel Blocker (NCCB); (3826:) NUAK family SNF1-like kinase 1 (AMPK-related protein kinase 5); (3827:) NUAK family SNF1-like kinase 2 (SNF1/AMP kinase-related kinase)(SNARK); (3828:) nuclear factor (erythroid-derived 2)-like 2 [Homo sapiens]; (3829:) nuclear factor kappa-B, subunit 1 [Homo sapiens]; (3830:) Nuclear Factor-Kappa B (NF-kB); (3831:) Nuclear receptor 0B1 (Nuclear receptor DAX-1) (DSS-AHC criticalregion on the X chromosome protein 1); (3832:) Nuclear receptor 0B2 (Orphan nuclear receptor SHP) (Smallheterodimer partner); (3833:) Nuclear receptor coactivator 3 (NCoA-3) (Thyroid hormone receptoractivator molecule 1) (TRAM-1) (ACTR) (Receptor-associatedcoactivator 3) (RAC-3) (Amplified in breast cancer-1 protein)(AIB-1) (Steroid receptor coactivator protein 3) (SRC-3)(CBP-interacting protein) (pCIP); (3834:) nuclear receptor interacting protein 1 [Homo sapiens]; (3835:) Nuclear receptor ROR-alpha (Nuclear receptor RZR-alpha); (3836:) Nuclear receptor ROR-beta (Nuclear receptor RZR-beta); (3837:) Nuclear receptor ROR-gamma (Nuclear receptor RZR-gamma); (3838:) nuclear receptor subfamily 1, group H, member 4 [Homo sapiens]; (3839:) nuclear receptor subfamily 3, group C, member 1 isoform alpha [Homosapiens]; (3840:) nuclear receptor subfamily 3, group C, member 1 isoform beta [Homosapiens]; (3841:) nuclear receptor subfamily 3, group C, member 1 isoform gamma [Homosapiens]; (3842:) nuclear receptor subfamily 5, group A, member 1 [Homo sapiens]; (3843:) nuclear receptor subfamily 5, group A, member 2 isoform 1 [Homosapiens]; (3844:) nuclear receptor subfamily 5, group A, member 2 isoform 2 [Homosapiens]; (3845:)

nucleolar protein GU2 [Homo sapiens]; (3846:) Nucleolin; (3847:) Nucleoside diphosphate kinase A (NDK A) (NDP kinase A) (Tumormetastatic process-associated protein) (Metastasis inhibitionfactor nm23) (nm23-H1) (Granzyme A-activated DNase) (GAAD); (3848:) Nucleoside diphosphate kinase B (NDK B) (NDP kinase B) (nm23-H2)(C-myc purine-binding transcription factor PUF); (3849:) Nucleoside Reverse Transcriptase (NRTI); (3850:) "nucleotide binding protein; NBP [Homo sapiens]."; (3851:) nudix -type motif 14 [Homo sapiens]; (3852:) nudix-type motif 1 isoform p18 [Homo sapiens]; (3853:) nudix-type motif 1 isoform p22 [Homo sapiens]; (3854:) nudix-type motif 2 [Homo sapiens]; (3855:) O6-Alkylguanine-DNA Alkyltransferase (AGT); (3856:) O-6-methylguanine-DNA methyltransferase; (3857:) OB-Cadherin; (3858:) Olfactory receptor 10A1 (Olfactory receptor 11-403) (OR11-403); (3859:) Olfactory receptor 10A3 (HTPCRX12); (3860:) Olfactory receptor 10A4 (HP2) (Olfactory receptor-like proteinJCG5); (3861:) Olfactory receptor 10A5 (HP3) (Olfactory receptor-like proteinJCG6); (3862:) Olfactory receptor 10A6; (3863:) Olfactory receptor 10A7; (3864:) Olfactory receptor 10AD1; (3865:) Olfactory receptor 10AG1 (Olfactory receptor OR11-160); (3866:) Olfactory receptor 10C1 (Hs6M1-17); (3867:) Olfactory receptor 10D4; (3868:) Olfactory receptor 10G2; (3869:) Olfactory receptor 10G3 (Olfactory receptor OR14-40); (3870:) Olfactory receptor 10G4 (Olfactory receptor OR11-278); (3871:) Olfactory receptor 10G6 (Olfactory receptor OR11-280); (3872:) Olfactory receptor 10G7; (3873:) Olfactory receptor 10G8 (Olfactory receptor OR11-282); (3874:) Olfactory receptor 10G9; (3875:) Olfactory receptor 10H1; (3876:) Olfactory receptor 10H2; (3877:) Olfactory receptor 10H3; (3878:) Olfactory receptor 10H4; (3879:) Olfactory receptor 10H5; (3880:) Olfactory receptor 10J1 (Olfactory receptor-like protein HGMP07J)(Olfactory receptor OR1-26); (3881:) Olfactory receptor 10J3; (3882:) Olfactory receptor 10J5; (3883:) Olfactory receptor 10J6; (3884:) Olfactory receptor 10K1; (3885:) Olfactory receptor 10K2 (Olfactory receptor OR1-4); (3886:) Olfactory receptor 10P1 (Olfactory receptor OR12-7); (3887:) Olfactory receptor 10Q1; (3888:) Olfactory receptor 10R2; (3889:) Olfactory receptor 10S1; (3890:) Olfactory receptor 10T2 (Olfactory receptor OR1-3); (3891:) Olfactory receptor 10V1; (3892:) Olfactory receptor 10W1 (Olfactory receptor OR11-236); (3893:) Olfactory receptor 10X1 (Olfactory receptor OR1-14); (3894:) Olfactory receptor 10Z1; (3895:) Olfactory receptor 11A1 (Hs6M1-18); (3896:) Olfactory receptor 11G2; (3897:) Olfactory receptor 11H1 (Olfactory receptor 22-1) (OR22-1); (3898:) Olfactory receptor 11H4 (Olfactory receptor OR14-36); (3899:) Olfactory receptor 11H6 (Olfactory receptor OR14-35); (3900:) Olfactory receptor 11L1; (3901:) Olfactory receptor 12D2

(Hs6M1-20); (3902:) Olfactory receptor 12D3 (Hs6M1-27); (3903:) Olfactory receptor 13A1 (Olfactory receptor OR10-3); (3904:) Olfactory receptor 13C2; (3905:) Olfactory receptor 13C3; (3906:) Olfactory receptor 13C4; (3907:) Olfactory receptor 13C5; (3908:) Olfactory receptor 13C8; (3909:) Olfactory receptor 13C9; (3910:) Olfactory receptor 13D1; (3911:) Olfactory receptor 13F1; (3912:) Olfactory receptor 13G1; (3913:) Olfactory receptor 13H1; (3914:) Olfactory receptor 13J1; (3915:) Olfactory receptor 1A1 (Olfactory receptor 17-7) (OR17-7)(Olfactory receptor OR17-11); (3916:) Olfactory receptor 1A2 (Olfactory receptor 17-6) (OR17-6)(Olfactory receptor OR17-10); (3917:) Olfactory receptor 1B1 (Olfactory receptor 9-B) (OR9-B) (Olfactoryreceptor OR9-26); (3918:) Olfactory receptor 1C1 (Olfactory receptor TPCR27) (Olfactoryreceptor OR1-42); (3919:) Olfactory receptor 1D2 (Olfactory receptor-like protein HGMP07E)(Olfactory receptor 17-4) (OR17-4); (3920:) Olfactory receptor 1D4 (Olfactory receptor 17-30) (OR17-30); (3921:) Olfactory receptor 1D5 (Olfactory receptor 17-31) (OR17-31); (3922:) Olfactory receptor 1E1 (Olfactory receptor-like protein HGMP07I)(Olfactory receptor 17-2/17-32) (OR17-2) (OR17-32) (Olfactoryreceptor 13-66) (OR13-66) (Olfactory receptor 5-85) (OR5-85); (3923:) Olfactory receptor 1E2 (Olfactory receptor 17-93/17-135/17-136)(OR17-93) (OR17-135) (OR17-136); (3924:) Olfactory receptor 1F1 (Olfactory receptor 16-35) (OR16-35)(Olfactory receptor OR16-4); (3925:) Olfactory receptor 1F10 (Olfactory receptor 3-145) (OR3-145); (3926:) Olfactory receptor 1F12 (Hs6M1-35P); (3927:) Olfactory receptor 1F2 (OLFmf2); (3928:) Olfactory receptor 1G1 (Olfactory receptor 17-209) (OR17-209); (3929:) Olfactory receptor 1I1 (Olfactory receptor 19-20) (OR19-20); (3930:) Olfactory receptor 1J1 (Olfactory receptor OR9-18); (3931:) Olfactory receptor 1J2 (OST044) (HSA5) (HTPCRX15) (Olfactoryreceptor OR9-19); (3932:) Olfactory receptor 1J4 (HTPCRX01) (Olfactory receptor OR9-21); (3933:) Olfactory receptor 1K1; (3934:) Olfactory receptor 1L1 (Olfactory receptor 9-C) (OR9-C); (3935:) Olfactory receptor 1L3 (Olfactory receptor 9-D) (OR9-D) (Olfactoryreceptor OR9-28); (3936:) Olfactory receptor 1L4 (Olfactory receptor 9-E) (OR9-E) (OST046); (3937:) Olfactory receptor 1L6; (3938:) Olfactory receptor 1L8 (Olfactory receptor OR9-24); (3939:) Olfactory receptor 1M1 (Olfactory receptor 19-6) (OR19-6); (3940:) Olfactory receptor 1N1 (Olfactory receptor 1-26) (OR1-26)(Olfactory receptor 1N3) (Olfactory receptor OR9-22); (3941:) Olfactory receptor 1N2; (3942:) Olfactory receptor 1Q1 (Olfactory receptor TPCR106) (Olfactoryreceptor 9-A) (OR9-A) (OST226) (Olfactory receptor OR9-25); (3943:) Olfactory receptor 1S1; (3944:) Olfactory receptor 1S2; (3945:) Olfactory receptor 2A12; (3946:) Olfactory receptor 2A14 (OST182); (3947:) Olfactory receptor 2A2

(Olfactory receptor OR7-11); (3948:) Olfactory receptor 2A4 (Olfactory receptor OR6-37); (3949:) Olfactory receptor 2A42; (3950:) Olfactory receptor 2A5 (Olfactory receptor 7-138/7-141) (OR7-138)(OR7-141); (3951:) Olfactory receptor 2A7; (3952:) Olfactory receptor 2AE1; (3953:) Olfactory receptor 2AG1 (HT3); (3954:) Olfactory receptor 2AJ1; (3955:) Olfactory receptor 2AK2 (Olfactory receptor OR1-47); (3956:) Olfactory receptor 2AP1 (Olfactory receptor OR12-9); (3957:) Olfactory receptor 2B11; (3958:) Olfactory receptor 2B2 (Olfactory receptor 6-1) (OR6-1) (Hs6M1-10); (3959:) Olfactory receptor 2B3 (Olfactory receptor 6-4) (OR6-4) (Olfactoryreceptor OR6-14) (Hs6M1-1); (3960:) Olfactory receptor 2B6 (Olfactory receptor 6-31) (OR6-31)(Olfactory receptor 5-40) (OR5-40) (Hs6M1-32); (3961:) Olfactory receptor 2B8 (Hs6M1-29P); (3962:) Olfactory receptor 2C1 (OLFmf3); (3963:) Olfactory receptor 2C3; (3964:) Olfactory receptor 2D2 (Olfactory receptor 11-610) (OR11-610) (HB2)(Olfactory receptor OR11-88); (3965:) Olfactory receptor 2D3; (3966:) Olfactory receptor 2F1 (Olfactory receptor-like protein OLF3); (3967:) Olfactory receptor 2F2 (Olfactory receptor 7-1) (OR7-1) (Olfactoryreceptor OR7-6); (3968:) Olfactory receptor 2G2 (Olfactory receptor OR1-32); (3969:) Olfactory receptor 2G3 (Olfactory receptor OR1-33); (3970:) Olfactory receptor 2G6; (3971:) Olfactory receptor 2H1 (Hs6M1-16) (Olfactory receptor 6-2) (OR6-2)(OLFR42A-9004.14/9026.2); (3972:) Olfactory receptor 2H2 (Hs6M1-12) (Olfactory receptor-like proteinFAT11); (3973:) Olfactory receptor 2H7 (OLFR42B-9079.6); (3974:) Olfactory receptor 2I1; (3975:) Olfactory receptor 2J1 (Olfactory receptor 6-5) (OR6-5) (Hs6M1-4); (3976:) Olfactory receptor 2J2 (Olfactory receptor 6-8) (OR6-8) (Hs6M1-6); (3977:) Olfactory receptor 2J3 (Olfactory receptor 6-6) (OR6-6) (Hs6M1-3); (3978:) Olfactory receptor 2K2 (HTPCRH06); (3979:) Olfactory receptor 2L13; (3980:) Olfactory receptor 2L2 (HTPCRH07); (3981:) Olfactory receptor 2L3; (3982:) Olfactory receptor 2L5 (Olfactory receptor OR1-53); (3983:) Olfactory receptor 2L8 (Olfactory receptor OR1-46); (3984:) Olfactory receptor 2M1 (Olfactory receptor-like protein JCG10)(OST037); (3985:) Olfactory receptor 2M2 (OST423); (3986:) Olfactory receptor 2M3 (Olfactory receptor OR1-54); (3987:) Olfactory receptor 2M4 (Olfactory receptor TPCR100) (OST710)(HTPCRX18) (Olfactory receptor OR1-55); (3988:) Olfactory receptor 2M7 (Olfactory receptor OR1-58); (3989:) Olfactory receptor 2S2 (Olfactory receptor OR9-3); (3990:) Olfactory receptor 2T1 (Olfactory receptor 1-25) (OR1-25)(Olfactory receptor OR1-61); (3991:) Olfactory receptor 2T10 (Olfactory receptor OR1-64); (3992:) Olfactory receptor 2T11 (Olfactory receptor OR1-65); (3993:) Olfactory receptor 2T12 (Olfactory receptor OR1-57); (3994:) Olfactory receptor 2T2 (Olfactory receptor OR1-43); (3995:) Olfactory

receptor 2T27 (Olfactory receptor OR1-67); (3996:) Olfactory receptor 2T29; (3997:) Olfactory receptor 2T3; (3998:) Olfactory receptor 2T33 (Olfactory receptor OR1-56); (3999:) Olfactory receptor 2T34 (Olfactory receptor OR1-63); (4000:) Olfactory receptor 2T35 (Olfactory receptor OR1-66); (4001:) Olfactory receptor 2T4 (Olfactory receptor OR1-60); (4002:) Olfactory receptor 2T5 (Olfactory receptor OR1-62); (4003:) Olfactory receptor 2T6 (OST703); (4004:) Olfactory receptor 2V2 (Olfactory receptor OR5-3); (4005:) Olfactory receptor 2W1 (Hs6M1-15); (4006:) Olfactory receptor 2W3 (Olfactory receptor OR1-49); (4007:) Olfactory receptor 2Y1 (Olfactory receptor OR5-2); (4008:) Olfactory receptor 2Z1 (Olfactory receptor OR19-4); (4009:) Olfactory receptor 3A1 (Olfactory receptor 17-40) (OR17-40); (4010:) Olfactory receptor 3A2 (Olfactory receptor 17-228) (OR17-228); (4011:) Olfactory receptor 3A3 (Olfactory receptor 17-201) (OR17-201); (4012:) Olfactory receptor 3A4 (Olfactory receptor 17-24) (OR17-24); (4013:) Olfactory receptor 4A15 (Olfactory receptor OR11-118); (4014:) Olfactory receptor 4A16 (Olfactory receptor OR11-117); (4015:) Olfactory receptor 4A4 (Olfactory receptor OR11-107); (4016:) Olfactory receptor 4A47 (Olfactory receptor OR11-113); (4017:) Olfactory receptor 4A5 (Olfactory receptor OR11-111); (4018:) Olfactory receptor 4B1 (OST208) (Olfactory receptor OR11-106); (4019:) Olfactory receptor 4C11 (Olfactory receptor OR11-136); (4020:) Olfactory receptor 4C12 (Olfactory receptor OR11-259); (4021:) Olfactory receptor 4C13 (Olfactory receptor OR11-260); (4022:) Olfactory receptor 4C15 (Olfactory receptor OR11-127) (Olfactoryreceptor OR11-134); (4023:) Olfactory receptor 4C16 (Olfactory receptor OR11-135); (4024:) Olfactory receptor 4C3 (Olfactory receptor OR11-98); (4025:) Olfactory receptor 4C5 (Olfactory receptor OR11-99); (4026:) Olfactory receptor 4C6 (Olfactory receptor OR11-138); (4027:) Olfactory receptor 4D1 (Olfactory receptor TPCR16); (4028:) Olfactory receptor 4D10 (Olfactory receptor OR11-251); (4029:) Olfactory receptor 4D11; (4030:) Olfactory receptor 4D2 (Olfactory receptor OR17-24) (B-lymphocytemembrane protein BC2009); (4031:) Olfactory receptor 4D5 (Olfactory receptor OR11-276); (4032:) Olfactory receptor 4D6 (Olfactory receptor OR11-250); (4033:) Olfactory receptor 4D9 (Olfactory receptor OR11-253); (4034:) Olfactory receptor 4E2 (Olfactory receptor OR14-42); (4035:) Olfactory receptor 4F14; (4036:) Olfactory receptor 4F15; (4037:) Olfactory receptor 4F17; (4038:) Olfactory receptor 4F29 (Olfactory receptor OR1-1); (4039:) Olfactory receptor 4F3; (4040:) Olfactory receptor 4F4 (HS14a-1-A) (Olfactory receptor OR19-3); (4041:) Olfactory receptor 4F5; (4042:) Olfactory receptor 4F6; (4043:) Olfactory receptor 4H12; (4044:) Olfactory receptor 4K1; (4045:) Olfactory receptor 4K13 (Olfactory receptor OR14-

27); (4046:) Olfactory receptor 4K14 (Olfactory receptor OR14-22); (4047:) Olfactory receptor 4K15; (4048:) Olfactory receptor 4K17; (4049:) Olfactory receptor 4K2; (4050:) Olfactory receptor 4K3; (4051:) Olfactory receptor 4K5; (4052:) Olfactory receptor 4L1 (Olfactory receptor OR14-28); (4053:) Olfactory receptor 4M1; (4054:) Olfactory receptor 4M2; (4055:) Olfactory receptor 4N2 (Olfactory receptor OR14-8); (4056:) Olfactory receptor 4N4; (4057:) Olfactory receptor 4N5 (Olfactory receptor OR14-33); (4058:) Olfactory receptor 4P4; (4059:) Olfactory receptor 4Q3 (Olfactory receptor OR14-3); (4060:) Olfactory receptor 4S1; (4061:) Olfactory receptor 4S2; (4062:) Olfactory receptor 4X1; (4063:) Olfactory receptor 4X2; (4064:) Olfactory receptor 51A2; (4065:) Olfactory receptor 51A4; (4066:) Olfactory receptor 51A7; (4067:) Olfactory receptor 51B2 (Odorant receptor HOR5'beta3); (4068:) Olfactory receptor 51B4 (Odorant receptor HOR5'beta1); (4069:) Olfactory receptor 51B5 (Odorant receptor HOR5'beta5) (Olfactoryreceptor OR11-37); (4070:) Olfactory receptor 51B5 (Odorant receptor HOR5'beta6); (4071:) Olfactory receptor 51D1 (Olfactory receptor OR11-14); (4072:) Olfactory receptor 51E1; (4073:) Olfactory receptor 51E2 (Prostate-specific G-protein coupledreceptor) (HPRAJ); (4074:) Olfactory receptor 51F2; (4075:) Olfactory receptor 51G1; (4076:) Olfactory receptor 51G2; (4077:) Olfactory receptor 51H1; (4078:) Olfactory receptor 51I1 (Odorant receptor HOR5'beta11) (Olfactoryreceptor OR11-39); (4079:) Olfactory receptor 51I2 (Odorant receptor HOR5'beta12) (Olfactoryreceptor OR11-38); (4080:) Olfactory receptor 51L1; (4081:) Olfactory receptor 51M1 (Odorant receptor HOR5'beta7) (Olfactoryreceptor OR11-40); (4082:) Olfactory receptor 51Q1; (4083:) Olfactory receptor 51S1; (4084:) Olfactory receptor 51T1; (4085:) Olfactory receptor 51V1 (Odorant receptor HOR3'beta1) (Olfactoryreceptor OR11-36); (4086:) Olfactory receptor 52A1 (HPFH1OR) (Odorant receptor HOR3'beta4); (4087:) Olfactory receptor 52A5 (Odorant receptor HOR3'beta5) (Olfactoryreceptor OR11-33); (4088:) Olfactory receptor 52B2; (4089:) Olfactory receptor 52B4 (Olfactory receptor OR11-3); (4090:) Olfactory receptor 52B6; (4091:) Olfactory receptor 52D1 (Odorant receptor HOR5'beta14) (Olfactoryreceptor OR11-43); (4092:) Olfactory receptor 52E1; (4093:) Olfactory receptor 52E2; (4094:) Olfactory receptor 52E4; (4095:) Olfactory receptor 52E5; (4096:) Olfactory receptor 52E6; (4097:) Olfactory receptor 52E8 (Olfactory receptor OR11-54); (4098:) Olfactory receptor 52H1; (4099:) Olfactory receptor 52I1; (4100:) Olfactory receptor 52I2; (4101:) Olfactory receptor 52J3; (4102:) Olfactory receptor 52K1; (4103:) Olfactory receptor 52K2; (4104:) Olfactory receptor 52L1; (4105:) Olfactory receptor 52L2; (4106:) Olfactory receptor 52M1 (Olfactory receptor OR11-11); (4107:) Olfactory receptor 52N1;

(4108:) Olfactory receptor 52N2; (4109:) Olfactory receptor 52N4; (4110:) Olfactory receptor 52N5; (4111:) Olfactory receptor 52P1; (4112:) Olfactory receptor 52R1; (4113:) Olfactory receptor 52W1 (Olfactory receptor OR11-71); (4114:) Olfactory receptor 56A1; (4115:) Olfactory receptor 56A3; (4116:) Olfactory receptor 56A4; (4117:) Olfactory receptor 56B1 (Olfactory receptor OR11-65); (4118:) Olfactory receptor 56B2; (4119:) Olfactory receptor 56B4; (4120:) Olfactory receptor 5A1 (OST181); (4121:) Olfactory receptor 5A2; (4122:) Olfactory receptor 5AC2 (HSA1); (4123:) Olfactory receptor 5AK2; (4124:) Olfactory receptor 5AK3; (4125:) Olfactory receptor 5AN1 (Olfactory receptor OR11-244); (4126:) Olfactory receptor 5AP2; (4127:) Olfactory receptor 5AR1; (4128:) Olfactory receptor 5AS1; (4129:) Olfactory receptor 5AT1; (4130:) Olfactory receptor 5AU1; (4131:) Olfactory receptor 5AV1; (4132:) Olfactory receptor 5AY1; (4133:) Olfactory receptor 5B12 (Olfactory receptor OR11-241); (4134:) Olfactory receptor 5B17 (Olfactory receptor OR11-237); (4135:) Olfactory receptor 5B2 (OST073) (Olfactory receptor OR11-240); (4136:) Olfactory receptor 5B3 (Olfactory receptor OR11-239); (4137:) Olfactory receptor 5BF1; (4138:) Olfactory receptor 5C1 (Olfactory receptor 9-F) (OR9-F); (4139:) Olfactory receptor 5D13; (4140:) Olfactory receptor 5D14; (4141:) Olfactory receptor 5D16; (4142:) Olfactory receptor 5D18; (4143:) Olfactory receptor 5F1 (Olfactory receptor 11-10) (OR11-10); (4144:) Olfactory receptor 5H2; (4145:) Olfactory receptor 5H6; (4146:) Olfactory receptor 5I1 (Olfactory receptor-like protein OLF1)(Olfactory receptor OR11-159); (4147:) Olfactory receptor 5J2 (Olfactory receptor OR11-266); (4148:) Olfactory receptor 5K1 (HTPCRX10); (4149:) Olfactory receptor 5K2 (Olfactory receptor OR3-9); (4150:) Olfactory receptor 5L1 (OST262); (4151:) Olfactory receptor 5L2 (HTPCRX16); (4152:) Olfactory receptor 5M1 (OST050); (4153:) Olfactory receptor 5M10 (Olfactory receptor OR11-207); (4154:) Olfactory receptor 5M11; (4155:) Olfactory receptor 5M3 (Olfactory receptor OR11-191); (4156:) Olfactory receptor 5M8 (Olfactory receptor OR11-194); (4157:) Olfactory receptor 5M9 (Olfactory receptor OR11-190); (4158:) Olfactory receptor 5P2 (Olfactory receptor-like protein JCG3); (4159:) Olfactory receptor 5P3 (Olfactory receptor-like protein JCG1); (4160:) Olfactory receptor 5R1 (Olfactory receptor OR11-185); (4161:) Olfactory receptor 5T1 (Olfactory receptor OR11-179); (4162:) Olfactory receptor 5T2; (4163:) Olfactory receptor 5T3; (4164:) Olfactory receptor 5U1 (Olfactory receptor OR6-25) (Hs6M1-28); (4165:) Olfactory receptor 5V1 (Hs6M1-21); (4166:) Olfactory receptor 5W2 (Olfactory receptor OR11-155); (4167:) Olfactory receptor 6A2 (Olfactory receptor 11-55) (OR11-55) (hP2olfactory receptor); (4168:) Olfactory receptor 6B1 (Olfactory receptor 7-3) (OR7-3); (4169:)

Olfactory receptor 6B2 (Olfactory receptor OR2-1); (4170:) Olfactory receptor 6B3 (Olfactory receptor OR2-2); (4171:) Olfactory receptor 6C1 (OST267); (4172:) Olfactory receptor 6C2 (HSA3); (4173:) Olfactory receptor 6C3 (HSA8); (4174:) Olfactory receptor 6C4; (4175:) Olfactory receptor 6F1 (Olfactory receptor OR1-38); (4176:) Olfactory receptor 6J1; (4177:) Olfactory receptor 6K2; (4178:) Olfactory receptor 6K3; (4179:) Olfactory receptor 6K6; (4180:) Olfactory receptor 6M1 (Olfactory receptor OR11-271); (4181:) Olfactory receptor 6N1; (4182:) Olfactory receptor 6N2; (4183:) Olfactory receptor 6P1 (Olfactory receptor OR1-12); (4184:) Olfactory receptor 6Q1; (4185:) Olfactory receptor 6S1; (4186:) Olfactory receptor 6T1; (4187:) Olfactory receptor 6V1; (4188:) Olfactory receptor 6W1 (Olfactory receptor sdolf); (4189:) Olfactory receptor 6X1 (Olfactory receptor OR11-270); (4190:) Olfactory receptor 6Y1 (Olfactory receptor OR1-11); (4191:) Olfactory receptor 7A10 (OST027) (Olfactory receptor OR19-18); (4192:) Olfactory receptor 7A17; (4193:) Olfactory receptor 7A2; (4194:) Olfactory receptor 7A5 (Olfactory receptor TPCR92); (4195:) Olfactory receptor 7C1 (Olfactory receptor TPCR86); (4196:) Olfactory receptor 7C2 (Olfactory receptor 19-18) (OR19-18); (4197:) Olfactory receptor 7D2 (Olfactory receptor 19-4) (OR19-4)(HTPCRH03); (4198:) Olfactory receptor 7D4 (Olfactory receptor OR19-7); (4199:) Olfactory receptor 7G1 (Olfactory receptor 19-15) (OR19-15); (4200:) Olfactory receptor 7G2 (Olfactory receptor 19-13) (OR19-13)(OST260); (4201:) Olfactory receptor 7G3 (OST085); (4202:) Olfactory receptor 8A1 (OST025); (4203:) Olfactory receptor 8B12 (Olfactory receptor OR11-317); (4204:) Olfactory receptor 8B2; (4205:) Olfactory receptor 8B3; (4206:) Olfactory receptor 8B4; (4207:) Olfactory receptor 8B8 (Olfactory receptor TPCR85) (Olfactory-likereceptor JCG8); (4208:) Olfactory receptor 8D1 (Olfactory receptor-like protein JCG9)(OST004) (Olfactory receptor OR11-301); (4209:) Olfactory receptor 8D2 (Olfactory receptor-like protein JCG2); (4210:) Olfactory receptor 8D4; (4211:) Olfactory receptor 8G1 (Olfactory receptor TPCR25) (Olfactoryreceptor OR11-281); (4212:) Olfactory receptor 8G2 (Olfactory receptor TPCR120) (Olfactoryreceptor OR11-297); (4213:) Olfactory receptor 8G5 (Olfactory receptor OR11-298); (4214:) Olfactory receptor 8H1; (4215:) Olfactory receptor 8H2; (4216:) Olfactory receptor 8H3; (4217:) Olfactory receptor 8I2; (4218:) Olfactory receptor 8J1; (4219:) Olfactory receptor 8J3; (4220:) Olfactory receptor 8K1; (4221:) Olfactory receptor 8K3; (4222:) Olfactory receptor 8K5; (4223:) Olfactory receptor 8S1; (4224:) Olfactory receptor 8U1; (4225:) Olfactory receptor 9A2; (4226:) Olfactory receptor 9A4; (4227:) Olfactory receptor 9G1; (4228:) Olfactory receptor 9G4; (4229:) Olfactory receptor 9G5 (Olfactory receptor OR11-114); (4230:)

Olfactory receptor 9I1; (4231:) Olfactory receptor 9K2; (4232:) Olfactory receptor 9Q1; (4233:) Olfactory receptor 9Q2; (4234:) olfactory receptor, family 4, subfamily F, member 6 [Homo sapiens]; (4235:) oligoadenylate synthetase; (4236:) O-linked GlcNAc transferase isoform 1 [Homo sapiens]; (4237:) O-linked GlcNAc transferase isoform 2 [Homo sapiens]; (4238:) Oncomodulin (OM) (Parvalbumin beta); (4239:) Opa-interacting protein OIP3 [Homo sapiens]; (4240:) Opioid Growth Factor Receptor (OGFr); (4241:) Opioid growth factor receptor (OGFr) (Zeta-type opioid receptor)(7-60 protein); (4242:) Opioid Receptor; (4243:) opioid receptor, mu 1 isoform MOR-1 [Homo sapiens]; (4244:) opioid receptor, mu 1 isoform MOR-1A [Homo sapiens]; (4245:) opioid receptor, mu 1 isoform MOR-1O [Homo sapiens]; (4246:) opioid receptor, mu 1 isoform MOR-1X [Homo sapiens]; (4247:) Opioid Receptor-Like1 (ORL1) Receptor; (4248:) Opsin-3 (Encephalopsin) (Panopsin); (4249:) Opsin-5 (Neuropsin) (G-protein coupled receptor 136) (G-proteincoupled receptor PGR12) (Transmembrane protein 13); (4250:) Orexigenic neuropeptide QRFP receptor (G-protein coupled receptor103) (SP9155) (AQ27); (4251:) Orexin Receptor; (4252:) Orexin receptor type 1 (Ox1r) (Hypocretin receptor type 1); (4253:) Orexin receptor type 2 (Ox2r) (Hypocretin receptor type 2); (4254:) Organic Anion Transporter 3 (OAT3); (4255:) Organic cation/carnitine transporter 1 (Solute carrier family 22member 4) (Ergothioneine transporter) (ET transporter); (4256:) ornithine aminotransferase precursor [Homo sapiens]; (4257:) ornithine carbamoyltransferase precursor [Homo sapiens]; (4258:) Ornithine carbamoyltransferase, mitochondrial precursor (OTCase)(Ornithine transcarbamylase); (4259:) Ornithine Decarboxylase; (4260:) ornithine decarboxylase 1 [Homo sapiens]; (4261:) ornithine decarboxylase-like protein [Homo sapiens]; (4262:) Orphan nuclear receptor EAR-2 (V-erbA-related protein EAR-2); (4263:) Orphan nuclear receptor NR1D1 (V-erbA-related protein EAR-1)(Rev-erbA-alpha); (4264:) Orphan nuclear receptor NR1D2 (Rev-erb-beta) (EAR-1R) (Orphannuclear hormone receptor BD73); (4265:) Orphan nuclear receptor NR1I3 (Constitutive androstane receptor)(CAR) (Constitutive activator of retinoid response) (Constitutiveactive response) (Orphan nuclear receptor MB67); (4266:) Orphan nuclear receptor NR2E1 (Nuclear receptor TLX) (Taillesshomolog) (Tll) (hTll); (4267:) Orphan nuclear receptor NR4A1 (Orphan nuclear receptor HMR) (Earlyresponse protein NAK1) (TR3 orphan receptor) (ST-59); (4268:) Orphan nuclear receptor NR4A2 (Orphan nuclear receptor NURR1)(Immediate-early response protein NOT) (Transcriptionally-induciblenuclear receptor); (4269:) Orphan nuclear receptor NR4A3 (Nuclear hormone receptor NOR-1)(Neuron-derived orphan

receptor 1) (Mitogen-induced nuclear orphanreceptor); (4270:) Orphan nuclear receptor NR5A2 (Alpha-1-fetoprotein transcriptionfactor) (Hepatocytic transcription factor) (B1-binding factor)(hB1F) (CYP7A promoter-binding factor) (Liver receptor homolog 1)(LRH-1); (4271:) Orphan nuclear receptor NR6A1 (Germ cell nuclear factor) (GCNF)(Retinoid receptor-related testis-specific receptor) (RTR); (4272:) Orphan nuclear receptor PXR (Pregnane X receptor) (Orphan nuclearreceptor PAR1) (Steroid and xenobiotic receptor) (SXR); (4273:) orphan nuclear receptor steroidogenic factor 1, SF-1(long terminalrepeat-binding protein, ELP) [human, Peptide, 205 aa]; (4274:) Orphan nuclear receptor TR2 (Testicular receptor 2); (4275:) Orphan nuclear receptor TR4 (Orphan nuclear receptor TAK1); (4276:) orphan UDP-glucuronosyltransferase (EC 2.4.-.-) - human; (4277:) OTU domain-containing protein 7B (Zinc finger protein Cezanne)(Zinc finger A20 domain-containing protein 1) (Cellular zinc fingeranti-NF-kappa B protein); (4278:) oxidised low density lipoprotein (lectin-like) receptor 1 [Homosapiens]; (4279:) Oxidized low-density lipoprotein receptor 1 (Ox-LDL receptor 1)(Lectin-type oxidized LDL receptor 1) (Lectin-like oxidized LDLreceptor 1) (Lectin-like oxLDL receptor 1) (LOX-1) (hLOX-1)[Contains:) Oxidized low-density lipoprotein receptor 1, solubleform]; (4280:) Oxidosqualene Cyclase (OSC); (4281:) Oxoeicosanoid receptor 1 (G-protein coupled receptor TG1019)(5-oxo-ETE G-protein coupled receptor) (G-protein coupled receptor170) (G-protein coupled receptor R527); (4282:) Oxysterols receptor LXR-alpha (Liver X receptor alpha) (Nuclearorphan receptor LXR-alpha); (4283:) Oxysterols receptor LXR-beta (Liver X receptor beta) (Nuclearorphan receptor LXR-beta) (Ubiquitously-expressed nuclear receptor)(Nuclear receptor NER); (4284:) Oxytocin Receptor (OTR); (4285:) oxytocin-neurophysin I preproprotein [Homo sapiens]; (4286:) P/Q-Type Calcium Channel Blocker; (4287:) p136 [Homo sapiens]; (4288:) P2 purinergic Receptor; (4289:) p21-activated kinase 2 [Homo sapiens]; (4290:) P2X purinoceptor 1 (ATP receptor) (P2X1) (Purinergic receptor); (4291:) P2X purinoceptor 2 (ATP receptor) (P2X2) (Purinergic receptor); (4292:) P2X purinoceptor 3 (ATP receptor) (P2X3) (Purinergic receptor); (4293:) P2X purinoceptor 4 (ATP receptor) (P2X4) (Purinergic receptor); (4294:) P2X purinoceptor 5 (ATP receptor) (P2X5) (Purinergic receptor); (4295:) P2X purinoceptor 6 (ATP receptor) (P2X6) (Purinergic receptor)(P2XM) (Purinergic receptor P2X-like 1); (4296:) P2X purinoceptor 7 (ATP receptor) (P2X7) (Purinergic receptor) (P2Zreceptor); (4297:) P2X3 Purinergic Receptor; (4298:) P2X7 Purinergic Receptor; (4299:) P2Y purinoceptor 1 (ATP receptor) (P2Y1) (Purinergic receptor); (4300:) P2Y purinoceptor 11 (P2Y11); (4301:) P2Y purinoceptor 12 (P2Y12) (P2Y12

platelet ADP receptor)(P2Y(ADP)) (ADP-glucose receptor) (ADPG-R) (P2Y(AC)) (P2Y(cyc))(P2T(AC)) (SP1999); (4302:) P2Y purinoceptor 13 (P2Y13) (G-protein coupled receptor 86)(G-protein coupled receptor 94); (4303:) P2Y purinoceptor 14 (P2Y14) (UDP-glucose receptor) (G-proteincoupled receptor 105); (4304:) P2Y purinoceptor 2 (P2Y2) (P2U purinoceptor 1) (P2U1) (ATPreceptor) (Purinergic receptor); (4305:) P2Y purinoceptor 4 (P2Y4) (Uridine nucleotide receptor) (UNR)(P2P); (4306:) P2Y purinoceptor 5 (P2Y5) (Purinergic receptor 5) (RB intronencoded G-protein coupled receptor); (4307:) P2Y purinoceptor 6 (P2Y6); (4308:) P2Y purinoceptor 8 (P2Y8); (4309:) P2Y12 Purinergic Receptor; (4310:) P2Y2 Purinergic Receptor; (4311:) p300/CBP-associated factor [Homo sapiens]; (4312:) p38 Mitogen-Activated Protein (MAP) Kinase; (4313:) p38 mitogen-activated protein (MAP) kinase activator; (4314:) p53 Activator; (4315:) p65 Protein; (4316:) p70 Ribosomal Protein S6 Kinase (S6K); (4317:) p85 beta subunit of phosphatidyl-inositol-3-kinase [Homo sapiens]; (4318:) Paired Box Gene 4 (Pax4) Functional; (4319:) Paired immunoglobulin-like type 2 receptor alpha precursor(Inhibitory receptor PILR-alpha) (Cell surface receptor FDF03); (4320:) Paired immunoglobulin-like type 2 receptor beta precursor(Activating receptor PILR-beta) (Cell surface receptor FDFACT); (4321:) palmitoyl-protein thioesterase [Homo sapiens]; (4322:) palmitoyl-protein thioesterase 1 (ceroid-lipofuscinosis, neuronal1, infantile) [Homo sapiens]; (4323:) Palmitoyl-protein thioesterase 1 precursor (PPT-1)(Palmitoyl-protein hydrolase 1); (4324:) PAN2 [Homo sapiens]; (4325:) pancreas-enriched phospholipase C [Homo sapiens]; (4326:) pancreatic ribonuclease precursor [Homo sapiens]; (4327:) Pantothenate kinase 1 (Pantothenic acid kinase 1) (hPanK1) (hPanK); (4328:) pantothenate kinase 1 isoform alpha [Homo sapiens]; (4329:) pantothenate kinase 1 isoform beta [Homo sapiens]; (4330:) pantothenate kinase 1 isoform gamma [Homo sapiens]; (4331:) pantothenate kinase 2 isoform 1 preproprotein [Homo sapiens]; (4332:) pantothenate kinase 2 isoform 2 [Homo sapiens]; (4333:) Pantothenate kinase 2, mitochondrial precursor (Pantothenic acidkinase 2) (hPANK2); (4334:) Pantothenate kinase 3 (Pantothenic acid kinase 3) (hPanK3); (4335:) pantothenate kinase 3 [Homo sapiens]; (4336:) Pantothenate kinase 4 (Pantothenic acid kinase 4) (hPanK4); (4337:) pantothenate kinase 4 [Homo sapiens]; (4338:) Pappalysin-1 precursor (Pregnancy-associated plasma protein-A)(PAPP-A) (Insulin-like growth factor-dependent IGF-binding protein4 protease) (IGF-dependent IGFBP-4 protease) (IGFBP-4ase); (4339:) PAPSS1 protein [Homo sapiens]; (4340:) paraoxanase-3 [Homo sapiens]; (4341:) paraoxonase 1 [Homo sapiens]; (4342:) paraoxonase 2 isoform 1 [Homo sapiens];

(4343:) paraoxonase 2 isoform 2 [Homo sapiens]; (4344:) paraoxonase 3 [Homo sapiens]; (4345:) Parathyroid Hormone (PTH); (4346:) Parathyroid hormone receptor precursor (PTH2 receptor); (4347:) Parathyroid hormone/parathyroid hormone-related peptide receptorprecursor (PTH/PTHr receptor) (PTH/PTHrP type I receptor); (4348:) parkin isoform 1 [Homo sapiens]; (4349:) parkin isoform 2 [Homo sapiens]; (4350:) parkin isoform 3 [Homo sapiens]; (4351:) PAS domain-containing serine/threonine-protein kinase (PAS-kinase)(PASKIN) (hPASK); (4352:) patatin-like phospholipase domain containing 1 isoform 2 [Homosapiens]; (4353:) patatin-like phospholipase domian containing 1 [Homo sapiens]; (4354:) PC Cell-Derived Growth Factor (PCDGF); (4355:) PC1/PC3 [Homo sapiens]; (4356:) PC8 precursor; (4357:) PCBD [Homo sapiens]; (4358:) PCK1 [Homo sapiens]; (4359:) PCK2 [Homo sapiens]; (4360:) PCTAIRE protein kinase 1 [Homo sapiens]; (4361:) PDC-E2 precursor (AA -54 to 561) [Homo sapiens]; (4362:) Pepsin; (4363:) Peptide Deformylase (PDF); (4364:) Peptide methionine sulfoxide reductase (Protein-methionine-S-oxidereductase) (PMSR) (Peptide Met(O) reductase); (4365:) Peptide-N(4)-(N-acetyl-beta-glucosaminyl)asparagine amidase(PNGase) (hPNGase) (Peptide:N-glycanase) (N-glycanase 1); (4366:) peptidyl arginine deiminase, type IV [Homo sapiens]; (4367:) peptidyl dipeptidase I [Homo sapiens]; (4368:) peptidylarginine deiminase type III [Homo sapiens]; (4369:) peptidylglycine alpha-amidating monooxygenase COOH-terminalinteractor [Homo sapiens]; (4370:) peptidylglycine alpha-amidating monooxygenase isoform a,preproprotein [Homo sapiens]; (4371:) peptidylglycine alpha-amidating monooxygenase isoform b,preproprotein [Homo sapiens]; (4372:) peptidylglycine alpha-amidating monooxygenase isoform c,preproprotein [Homo sapiens]; (4373:) peptidylglycine alpha-amidating monooxygenase isoform d,preproprotein [Homo sapiens]; (4374:) "Peptidyl-glycine alpha-amidating monooxygenase precursor (PAM)[Includes:) Peptidylglycine alpha-hydroxylating monooxygenase (PHM);Peptidyl-alpha-hydroxyglycine alpha-amidating lyase(Peptidylamidoglycolate lyase) (PAL)]."; (4375:) Peptidylprolyl Cis-Trans Isomerase (PPlase); (4376:) Peptidyl-prolyl cis-trans isomerase A (PPlase A) (Rotamase A)(Cyclophilin A) (Cyclosporin A-binding protein); (4377:) Peptidyl-prolyl cis-trans isomerase B precursor (PPlase) (Rotamase)(Cyclophilin B) (S-cyclophilin) (SCYLP) (CYP-S1); (4378:) Peptidyl-prolyl cis-trans isomerase C (PPlase) (Rotamase)(Cyclophilin C); (4379:) Peptidyl-prolyl cis-trans isomerase G (Peptidyl-prolyl isomerase G)(PPlase G) (Rotamase G) (Cyclophilin G) (Clk-associatingRS-cyclophilin) (CARS-cyclophilin) (CARS-Cyp) (SR-cyclophilin)(SRcyp) (SR-cyp) (CASP10); (4380:) Peptidyl-prolyl cis-trans

isomerase-like 1 (PPIase) (Rotamase); (4381:) peptidylprolyl isomerase A [Homo sapiens]; (4382:) Peptidyl-tRNA hydrolase 2, mitochondrial precursor (PTH 2) (Bcl-2inhibitor of transcription 1); (4383:) Peripheral Chemoreceptor; (4384:) Peripheral-type benzodiazepine receptor (PBR) (PKBS) (Mitochondrialbenzodiazepine receptor); (4385:) peroxiredoxin 2 isoform a [Homo sapiens]; (4386:) peroxiredoxin 2 isoform c [Homo sapiens]; (4387:) peroxiredoxin 5 precursor, isoform a [Homo sapiens]; (4388:) peroxiredoxin 5 precursor, isoform b [Homo sapiens]; (4389:) peroxiredoxin 5 precursor, isoform c [Homo sapiens]; (4390:) peroxiredoxin 6 [Homo sapiens]; (4391:) Peroxiredoxin-1 (Thioredoxin peroxidase 2) (Thioredoxin-dependentperoxide reductase 2) (Proliferation-associated protein PAG)(Natural killer cell-enhancing factor A) (NKEF-A); (4392:) Peroxiredoxin-2 (Thioredoxin peroxidase 1) (Thioredoxin-dependentperoxide reductase 1) (Thiol-specific antioxidant protein) (TSA)(PRP) (Natural killer cell-enhancing factor B) (NKEF-B); (4393:) Peroxiredoxin-4 (Prx-IV) (Thioredoxin peroxidase AO372)(Thioredoxin-dependent peroxide reductase A0372) (Antioxidantenzyme AOE372) (AOE37-2); (4394:) Peroxiredoxin-5, mitochondrial precursor (Prx-V) (Peroxisomalantioxidant enzyme) (PLP) (Thioredoxin reductase) (Thioredoxinperoxidase PMP20) (Antioxidant enzyme B166) (AOEB166) (TPx type VI)(Liver tissue 2D-page spot 71B) (Alu corepressor 1); (4395:) Peroxiredoxin-6 (Antioxidant protein 2) (1-Cys peroxiredoxin)(1-Cys PRX) (Acidic calcium-independent phospholipase A2) (aiPLA2)(Non-selenium glutathione peroxidase) (NSGPx) (24 kDa protein)(Liver 2D page spot 40) (Red blood cells page spot 12); (4396:) Peroxisomal 2,4-dienoyl-CoA reductase (2,4-dienoyl-CoA reductase 2)(pDCR); (4397:) peroxisomal acyl-CoA thioesterase 1 isoform a [Homo sapiens]; (4398:) peroxisomal acyl-CoA thioesterase 1 isoform c [Homo sapiens]; (4399:) "Peroxisomal bifunctional enzyme (PBE) (PBFE) [Includes:) Enoyl-CoAhydratase ; 3,2-trans-enoyl-CoA isomerase ; 3-hydroxyacyl-CoAdehydrogenase]."; (4400:) Peroxisomal coenzyme A diphosphatase NUDT7 (Nucleosidediphosphate-linked moiety X motif 7) (Nudix motif 7); (4401:) peroxisomal D3,D2-enoyl-CoA isomerase isoform 1 [Homo sapiens]; (4402:) peroxisomal D3,D2-enoyl-CoA isomerase isoform 2 [Homo sapiens]; (4403:) peroxisomal enoyl-coenzyme A hydratase-like protein [Homo sapiens]; (4404:) Peroxisomal multifunctional enzyme type 2 (MFE-2) (D-bifunctionalprotein) (DBP) (17-beta-hydroxysteroid dehydrogenase 4)(17-beta-HSD 4) (D-3-hydroxyacyl-CoA dehydratase)(3-alpha,7-alpha,12-alpha-trihydroxy-5-beta-cholest-24-enoyl-CoAhydratase) (3-hydroxyacyl-CoA dehydrogenase); (4405:) Peroxisomal NADH pyrophosphatase NUDT12 (Nucleosidediphosphate-linked

moiety X motif 12) (Nudix motif 12); (4406:) Peroxisomal sarcosine oxidase (PSO) (L-pipecolate oxidase)(L-pipecolic acid oxidase); (4407:) Peroxisomal trans-2-enoyl-CoA reductase (TERP) (HPDHase) (pVI-ARL)(2,4-dienoyl-CoA reductase-related protein) (DCR-RP); (4408:) peroxisome proliferative activated receptor gamma isoform 1 [Homosapiens]; (4409:) peroxisome proliferative activated receptor gamma isoform 2 [Homosapiens]; (4410:) Peroxisome proliferator-activated receptor alpha (PPAR-alpha); (4411:) Peroxisome proliferator-activated receptor delta (PPAR-delta)(PPAR-beta) (Nuclear hormone receptor 1) (NUC1) (NUCI); (4412:) Peroxisome proliferator-activated receptor gamma (PPAR-gamma); (4413:) peroxisome proliferator-activated receptor gamma, coactivator 1alpha [Homo sapiens]; (4414:) peroxisome proliferator-activated receptor gamma-2 - human; (4415:) Peroxisome Proliferator-Activated Receptor-Alpha (PPAR-Alpha); (4416:) Peroxisome Proliferator-Activated Receptor-Delta (PPAR-Delta); (4417:) Peroxisome proliferator-activated receptor-gamma (PPAR-gamma) Partial; (4418:) PFKL protein [Homo sapiens]; (4419:) PFKM [Homo sapiens]; (4420:) PFKM protein [Homo sapiens]; (4421:) PFKP protein [Homo sapiens]; (4422:) PGK1 [Homo sapiens]; (4423:) P-Glycoprotein (P-gp); (4424:) PH domain leucine-rich repeat-containing protein phosphatase (PHdomain leucine-rich repeat protein phosphatase) (Pleckstrinhomology domain-containing family E protein 1) (Suprachiasmaticnucleus circadian oscillatory protein) (hSCOP); (4425:) phenylalanine hydroxylase [Homo sapiens]; (4426:) phenylalanine hydroxylase-stimulating protein, pterin-4alpha-carbinolamine dehydratase, PHS, PCD [human, liver, Peptide,103 aa]; (4427:) Phenylalanine-4-hydroxylase (PAH) (Phe-4-monooxygenase); (4428:) Phenylethanolamine N-methyltransferase (PNMTase) (NoradrenalineN-methyltransferase); (4429:) phenylethanolamine N-methyltransferase [Homo sapiens]; (4430:) phenylethanolamine N-methyltransferase; (4431:) phosphate cytidylyltransferase 1, choline, alpha isoform [Homosapiens]; (4432:) phosphatidate cytidylyltransferase 1 [Homo sapiens]; (4433:) phosphatidate cytidylyltransferase 2 [Homo sapiens]; (4434:) phosphatidic acid phosphatase type 2 domain containing 2 [Homosapiens]; (4435:) phosphatidic acid phosphatase type 2A isoform 1 [Homo sapiens]; (4436:) phosphatidic acid phosphatase type 2A isoform 2 [Homo sapiens]; (4437:) Phosphatidylcholine (PtdCho) Synthesis; (4438:) Phosphatidylcholine:ceramide cholinephosphotransferase 1(Transmembrane protein 23) (Sphingomyelin synthase 1) (Mobprotein); (4439:) Phosphatidylcholine:ceramide cholinephosphotransferase 2(Sphingomyelin synthase 2); (4440:) Phosphatidylcholine-sterol acyltransferase precursor(Lecithin-

cholesterol acyltransferase) (Phospholipid-cholesterolacyltransferase); (4441:) Phosphatidylethanolamine N-methyltransferase (PEAMT) (PEMT)(PEMT2); (4442:) phosphatidylethanolamine N-methyltransferase isoform 1 [Homosapiens]; (4443:) phosphatidylethanolamine N-methyltransferase isoform 2 [Homosapiens]; (4444:) Phosphatidylinositol 3-Kinase (PI3K); (4445:) Phosphatidylinositol 3-kinase catalytic subunit type 3(PtdIns-3-kinase type 3) (PI3-kinase type 3) (PI3K type 3)(Phosphoinositide-3-kinase class 3) (Phosphatidylinositol 3-kinasep100 subunit); (4446:) Phosphatidylinositol 3-kinase regulatory subunit beta (PI3-kinasep85-subunit beta) (PtdIns-3-kinase p85-beta); (4447:) Phosphatidylinositol 4-kinase alpha (PI4-kinase alpha)(PtdIns-4-kinase alpha) (PI4K-alpha); (4448:) Phosphatidylinositol 4-kinase beta (PtdIns 4-kinase beta)(PI4Kbeta) (PI4K-beta) (NPIK) (PI4K92); (4449:) phosphatidylinositol 4-kinase type II [Homo sapiens]; (4450:) phosphatidylinositol 4-kinase type-II beta [Homo sapiens]; (4451:) phosphatidylinositol 4-kinase, catalytic, alpha polypeptide isoform1 [Homo sapiens]; (4452:) phosphatidylinositol 4-kinase, catalytic, alpha polypeptide isoform2 [Homo sapiens]; (4453:) phosphatidylinositol 4-kinase, catalytic, beta polypeptide [Homosapiens]; (4454:) phosphatidylinositol glycan anchor biosynthesis, class K precursor[Homo sapiens]; (4455:) phosphatidylinositol glycan anchor biosynthesis, class L [Homosapiens]; (4456:) phosphatidylinositol glycan anchor biosynthesis, class P isoform 1[Homo sapiens]; (4457:) phosphatidylinositol glycan anchor biosynthesis, class P isoform 2[Homo sapiens]; (4458:) phosphatidylinositol glycan anchor biosynthesis, class Q isoform 1[Homo sapiens]; (4459:) phosphatidylinositol glycan anchor biosynthesis, class Q isoform 2[Homo sapiens]; (4460:) phosphatidylinositol glycan anchor biosynthesis, class S [Homosapiens]; (4461:) phosphatidylinositol glycan anchor biosynthesis, class T precursor[Homo sapiens]; (4462:) phosphatidylinositol glycan anchor biosynthesis, class Y isoform 1[Homo sapiens]; (4463:) phosphatidylinositol glycan anchor biosynthesis, class Y isoform 2[Homo sapiens]; (4464:) phosphatidylinositol glycan class Y [Homo sapiens]; (4465:) phosphatidylinositol glycan, class C [Homo sapiens]; (4466:) Phosphatidylinositol N-acetylglucosaminyltransferase subunit A(GlcNAc-PI synthesis protein) (Phosphatidylinositol-glycanbiosynthesis class A protein) (PIG-A); (4467:) phosphatidylinositol N-acetylglucosaminyltransferase subunit Aisoform 1 [Homo sapiens]; (4468:) phosphatidylinositol N-acetylglucosaminyltransferase subunit Aisoform 3 [Homo sapiens]; (4469:) Phosphatidylinositol N-acetylglucosaminyltransferase subunit P(Phosphatidylinositol-glycan biosynthesis class P protein) (PIG-P)(Down syndrome critical region protein 5) (Down syndrome criticalregion protein C); (4470:)

Phosphatidylinositol N-acetylglucosaminyltransferase subunit Q(Phosphatidylinositol-glycan biosynthesis class Q protein) (PIG-Q)(N-acetylglucosamyl transferase component GPI1); (4471:) Phosphatidylinositol N-acetylglucosaminyltransferase subunit Y(Phosphatidylinositol-glycan biosynthesis class Y protein) (PIG-Y); (4472:) phosphatidylinositol polyphosphate 5-phosphatase isoform a [Homosapiens]; (4473:) phosphatidylinositol polyphosphate 5-phosphatase isoform b [Homosapiens]; (4474:) Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunitgamma isoform (PI3-kinase p110 subunit gamma) (PtdIns-3-kinasesubunit p110) (PI3K) (PI3Kgamma) (p120-PI3K); (4475:) Phosphatidylinositol-4-phosphate 3-kinase C2 domain-containing betapolypeptide (Phosphoinositide 3-Kinase-C2-beta) (PtdIns-3-kinase C2beta) (PI3K-C2beta) (C2-PI3K); (4476:) Phosphatidylinositol-4-phosphate 3-kinase C2 domain-containingalpha polypeptide (Phosphoinositide 3-Kinase-C2-alpha)(PtdIns-3-kinase C2 alpha) (PI3K-C2alpha); (4477:) phosphatidylinositol-4-phosphate 5-kinase type II alpha [Homosapiens]; (4478:) Phosphatidylinositol-4-phosphate 5-kinase type-1 gamma(Phosphatidylinositol-4-phosphate 5-kinase type I gamma)(PtdIns(4)P-5-kinase gamma) (PtdInsPKIgamma) (PIP5KIgamma); (4479:) phosphatidylinositol-4-phosphate 5-kinase, type I, alpha [Homosapiens]; (4480:) phosphatidylinositol-4-phosphate 5-kinase, type I, gamma [Homosapiens]; (4481:) Phosphatidylserine Receptor (PTDSR); (4482:) Phosphatidylserine synthase 1 (PtdSer synthase 1) (PSS-1)(Serine-exchange enzyme I); (4483:) Phosphatidylserine synthase 2 (PtdSer synthase 2) (PSS-2)(Serine-exchange enzyme II); (4484:) Phosphodiesterase (PDE); (4485:) phosphodiesterase 5A isoform 1 [Homo sapiens]; (4486:) phosphodiesterase 5A isoform 2 [Homo sapiens]; (4487:) phosphodiesterase 5A isoform 3 [Homo sapiens]; (4488:) phosphodiesterase 6B, cGMP-specific, rod, beta [Homo sapiens]; (4489:) phosphodiesterase 8A isoform 1 [Homo sapiens]; (4490:) phosphodiesterase 8A isoform 2 [Homo sapiens]; (4491:) phosphodiesterase 8A isoform 3 [Homo sapiens]; (4492:) phosphodiesterase 8A isoform 4 [Homo sapiens]; (4493:) phosphodiesterase I/nucleotide pyrophosphatase beta [Homo sapiens]; (4494:) Phosphodiesterase-1 (PDE-1); (4495:) Phosphodiesterase-10A (PDE-10A); (4496:) Phosphodiesterase-2 (PDE-2); (4497:) Phosphodiesterase-3 (PDE-3); (4498:) Phosphodiesterase-4 (PDE-4); (4499:) Phosphodiesterase-5 (PDE-5); (4500:) Phosphodiesterase-5 (PDE-5); (4501:) phosphoenolpyruvate carboxykinase (GTP) [Homo sapiens]; (4502:) Phosphoenolpyruvate carboxykinase [GTP], mitochondrial precursor(Phosphoenolpyruvate carboxylase) (PEPCK-M); (4503:) Phosphoenolpyruvate carboxykinase 1 (soluble) [Homo sapiens]; (4504:)

Phosphoenolpyruvate carboxykinase 2 (mitochondrial) [Homo sapiens]; (4505:) Phosphoenolpyruvate carboxykinase, cytosolic [GTP](Phosphoenolpyruvate carboxylase) (PEPCK-C); (4506:) phosphoenolpyruvate carboxykinase; (4507:) Phosphoethanolamine/phosphocholine phosphatase; (4508:) phosphofructokinase [Homo sapiens]; (4509:) Phosphofructokinase, liver [Homo sapiens]; (4510:) phosphofructokinase, muscle [Homo sapiens]; (4511:) phosphofructokinase, platelet [Homo sapiens]; (4512:) phosphofructokinase; (4513:) phosphofructokinase-M; (4514:) phosphofructokinase-P [Homo sapiens]; (4515:) phosphoglucomutase 1 [Homo sapiens]; (4516:) Phosphoglucomutase-1 (Glucose phosphomutase 1) (PGM 1); (4517:) Phosphoglucomutase-2 (Glucose phosphomutase 2) (PGM 2); (4518:) phosphogluconate dehydrogenase [Homo sapiens]; (4519:) phosphoglycerate dehydrogenase [Homo sapiens]; (4520:) phosphoglycerate kinase [Homo sapiens]; (4521:) Phosphoglycerate kinase 1 (Primer recognition protein 2) (PRP 2); (4522:) phosphoglycerate kinase 1 [Homo sapiens]; (4523:) Phosphoglycerate kinase 2 [Homo sapiens]; (4524:) Phosphoglycerate kinase, testis specific; (4525:) phosphoglycerete kinase 1 [Homo sapiens]; (4526:) phosphoinositide 3-kinase (EC 2.7.-.-) T105 - human (fragment); (4527:) phosphoinositide 3-kinase (EC 2.7.-.-) T14 - human (fragment); (4528:) Phosphoinositide 3-kinase regulatory subunit 5 (PI3-kinaseregulatory subunit 5) (PI3-kinase p101 subunit) (PtdIns-3-kinasep101) (p101-PI3K) (Phosphatidylinositol-4,5-bisphosphate 3-kinaseregulatory subunit) (PtdIns-3-kinase regulatory subunit) (ProteinFOAP-2); (4529:) phosphoinositide-3-kinase, catalytic, alpha polypeptide [Homosapiens]; (4530:) phosphoinositide-3-kinase, catalytic, beta polypeptide [Homosapiens]; (4531:) phosphoinositide-3-kinase, catalytic, gamma polypeptide [Homosapiens]; (4532:) phosphoinositide-3-kinase, class 2, beta polypeptide [Homosapiens]; (4533:) phosphoinositide-3-kinase, class 3 [Homo sapiens]; (4534:) phosphoinositide-3-kinase, regulatory subunit 2 (p85 beta) [Homosapiens]; (4535:) phosphoinositide-3-kinase, regulatory subunit, polypeptide 1isoform 1 [Homo sapiens]; (4536:) phosphoinositide-3-kinase, regulatory subunit, polypeptide 1isoform 2 [Homo sapiens]; (4537:) phosphoinositide-3-kinase, regulatory subunit, polypeptide 1isoform 3 [Homo sapiens]; (4538:) phosphoinositide-specific phospholipase C PLC-epsilon [Homosapiens]; (4539:) phospholemman precursor [Homo sapiens]; (4540:) Phospholipase A2 (PLA2); (4541:) Phospholipase A2 precursor (Phosphatidylcholine 2-acylhydrolase)(Group IB phospholipase A2); (4542:) phospholipase A2, group IIA [Homo sapiens]; (4543:) phospholipase A2, group IIE [Homo sapiens]; (4544:) phospholipase A2, group III precursor [Homo sapiens];

(4545:) phospholipase A2, group V precursor [Homo sapiens]; (4546:) phospholipase A2, group VI isoform a [Homo sapiens]; (4547:) phospholipase A2, group VI isoform b [Homo sapiens]; (4548:) phospholipase A2, group VII [Homo sapiens]; (4549:) Phospholipase A2, membrane associated precursor(Phosphatidylcholine 2-acylhydrolase) (Group IIA phospholipase A2)(GIIC sPLA2) (Non-pancreatic secretory phospholipase A2)(NPS-PLA2); (4550:) phospholipase A2; (4551:) phospholipase C delta 3 [Homo sapiens]; (4552:) phospholipase C epsilon [Homo sapiens]; (4553:) phospholipase C epsilon 1 [Homo sapiens]; (4554:) phospholipase C gamma 1 isoform a [Homo sapiens]; (4555:) phospholipase C gamma 1 isoform b [Homo sapiens]; (4556:) phospholipase C, delta 1 [Homo sapiens]; (4557:) phospholipase C, delta 4 [Homo sapiens]; (4558:) phospholipase C, epsilon 1 [Homo sapiens]; (4559:) phospholipase C-eta2 [Homo sapiens]; (4560:) Phospholipase D1 (PLD 1) (Choline phosphatase 1)(Phosphatidylcholine-hydrolyzing phospholipase D1) (hPLD1); (4561:) Phospholipase D2 (PLD 2) (Choline phosphatase 2)(Phosphatidylcholine-hydrolyzing phospholipase D2) (PLD1C) (hPLD2); (4562:) phospholipid scramblase 1 [Homo sapiens]; (4563:) phospholipid transfer protein isoform a precursor [Homo sapiens]; (4564:) phospholipid transfer protein isoform b precursor [Homo sapiens]; (4565:) phospholysine phosphohistidine inorganic pyrophosphate phosphatase(EC 3.6.1.1) - Human; (4566:) phosphomevalonate kinase [Homo sapiens]; (4567:) phosphopantetheine adenylyltransferase / dephosphocoenzyme A kinase[Homo sapiens]; (4568:) Phosphopantothenate--cysteine ligase (Phosphopantothenoylcysteinesynthetase) (PPC synthetase); (4569:) phosphoprotein phosphatase (EC 3.1.3.16) 2A BR gamma regulatorychain - human; (4570:) phosphoribosyl pyrophosphate amidotransferase proprotein [Homosapiens]; (4571:) phosphoribosyl pyrophosphate synthetase-associated protein 2 [Homosapiens]; (4572:) phosphoribosylformylglycinamidine synthase [Homo sapiens]; (4573:) phosphoribosylglycinamide formyltransferase,phosphoribosylglycinamide synthetase, phosphoribosylaminoimidazolesynthetase isoform 1 [Homo sapiens]; (4574:) phosphoribosylglycinamide formyltransferase,phosphoribosylglycinamide synthetase, phosphoribosylaminoimidazolesynthetase isoform 2 [Homo sapiens]; (4575:) phosphoribosylpyrophosphate synthetase subunit III; (4576:) Phosphorylase b kinase regulatory subunit alpha, liver isoform(Phosphorylase kinase alpha L subunit); (4577:) Phosphorylase b kinase regulatory subunit alpha, skeletal muscleisoform (Phosphorylase kinase alpha M subunit); (4578:) Phosphorylase b

kinase regulatory subunit beta (Phosphorylasekinase subunit beta); (4579:) phosphorylase kinase gamma subunit 1 [Homo sapiens]; (4580:) phosphorylase kinase, alpha 1 (muscle) [Homo sapiens]; (4581:) phosphoserine aminotransferase isoform 1 [Homo sapiens]; (4582:) phosphoserine aminotransferase isoform 2 [Homo sapiens]; (4583:) Phosphoserine phosphatase (PSP) (O-phosphoserine phosphohydrolase)(PSPase) (L-3-phosphoserine phosphatase); (4584:) phosphoserine phosphatase [Homo sapiens]; (4585:) photoreceptor outer segment all-trans retinol dehydrogenase [Homosapiens]; (4586:) Photoreceptor-specific nuclear receptor (Retina-specific nuclearreceptor); (4587:) phytanoil-CoA alpha hydroxylase [Homo sapiens]; (4588:) phytanoyl-CoA 2-hydroxylase isoform a precursor [Homo sapiens]; (4589:) phytanoyl-CoA 2-hydroxylase isoform b precursor [Homo sapiens]; (4590:) Phytanoyl-CoA dioxygenase, peroxisomal precursor (Phytanoyl-CoAalpha-hydroxylase) (PhyH) (Phytanic acid oxidase); (4591:) phytoceramidase, alkaline [Homo sapiens]; (4592:) PI-3 kinase [Homo sapiens]; (4593:) PIG50 [Homo sapiens]; (4594:) pim-1 oncogene [Homo sapiens]; (4595:) Pim-1 Receptor Tyrosine Kinase; (4596:) PITSLRE serine/threonine-protein kinase CDC2L1(Galactosyltransferase-associated protein kinase p58/GTA) (Celldivision cycle 2-like protein kinase 1) (CLK-1) (CDK11) (p58CLK-1); (4597:) PITSLRE serine/threonine-protein kinase CDC2L2(Galactosyltransferase-associated protein kinase p58/GTA) (Celldivision cycle 2-like protein kinase 2) (CDK11); (4598:) Pituitary Adenylate Cyclase Activating Peptide Receptor 3 (PACAP R3); (4599:) pituitary adenylate cyclase activating peptide receptor type Iprecursor - human; (4600:) Pituitary adenylate cyclase-activating polypeptide type I receptorprecursor (PACAP type I receptor) (PACAP-R-1); (4601:) PKM2 protein [Homo sapiens]; (4602:) placenta copper monamine oxidase [Homo sapiens]; (4603:) Placental Alkaline Phosphatase (PALP); (4604:) placental alkaline phosphatase preproprotein [Homo sapiens]; (4605:) placental lactogen hormone precursor [Homo sapiens]; (4606:) placental lactogen; (4607:) placental-like alkaline phosphatase preproprotein [Homo sapiens]; (4608:) plakoglobin [Homo sapiens]; (4609:) plasma carboxypeptidase B2 isoform a preproprotein [Homo sapiens]; (4610:) plasma carboxypeptidase B2 isoform b [Homo sapiens]; (4611:) plasma glutathione peroxidase 3 precursor [Homo sapiens]; (4612:) plasma kallikrein B1 precursor [Homo sapiens]; (4613:) "Plasma kallikrein precursor (Plasma prekallikrein) (Kininogenin)(Fletcher factor) [Contains:) Plasma kallikrein heavy chain; Plasmakallikrein light chain]."; (4614:) Plasma membrane calcium-transporting ATPase 1 (PMCA1) (Plasmamembrane calcium pump isoform 1)

(Plasma membrane calcium ATPaseisoform 1); (4615:) Plasma membrane calcium-transporting ATPase 2 (PMCA2) (Plasmamembrane calcium pump isoform 2) (Plasma membrane calcium ATPaseisoform 2); (4616:) Plasma membrane calcium-transporting ATPase 3 (PMCA3) (Plasmamembrane calcium pump isoform 3) (Plasma membrane calcium ATPaseisoform 3); (4617:) Plasma membrane calcium-transporting ATPase 4 (PMCA4) (Plasmamembrane calcium pump isoform 4) (Plasma membrane calcium ATPaseisoform 4); (4618:) plasminogen [Homo sapiens]; (4619:) Plasminogen activator (PAI); (4620:) Plasminogen activator -1 (PAI-1); (4621:) plasminogen activator, tissue type isoform 1 preproprotein [Homosapiens]; (4622:) plasminogen activator, tissue type isoform 2 precursor [Homosapiens]; (4623:) plasminogen activator, tissue type isoform 3 precursor [Homosapiens]; (4624:) plasminogen activator, urokinase receptor isoform 1 precursor [Homosapiens]; (4625:) plasminogen activator, urokinase receptor isoform 2 precursor [Homosapiens]; (4626:) plasminogen activator, urokinase receptor isoform 3 precursor [Homosapiens]; (4627:) "Plasminogen precursor [Contains:) Plasmin heavy chain A; Activationpeptide; Angiostatin; Plasmin heavy chain A, short form; Plasminlight chain B]."; (4628:) Plasmodium Falciparum Calcium-Dependent ATPase (PfATP6); (4629:) platelet coagulation factor XI isoform b [Homo sapiens]; (4630:) platelet coagulation factor XI precursor [Homo sapiens]; (4631:) Platelet Derived Growth Factor Receptor-Alpha (PDGFR-Alpha); (4632:) Platelet Derived Growth Factor Receptor-Beta (PDGFR-Beta); (4633:) platelet factor 4 (chemokine (C-X-C motif) ligand 4) [Homosapiens]; (4634:) Platelet glycoprotein 4 (Platelet glycoprotein IV) (GPIV)(Glycoprotein IIIb) (GPIIIB) (Leukocyte differentiation antigenCD36) (CD36 antigen) (PAS IV) (PAS-4 protein) (Platelet collagenreceptor) (Fatty acid translocase) (FAT) (Thrombospondin receptor); (4635:) Platelet glycoprotein VI precursor; (4636:) Platelet receptor Gi24 precursor; (4637:) Platelet-Activating Factor (PAF); (4638:) platelet-activating factor acetylhydrolase 2 [Homo sapiens]; (4639:) Platelet-activating factor acetylhydrolase 2, cytoplasmic(Serine-dependent phospholipase A2) (HSD-PLA2); (4640:) Platelet-activating factor acetylhydrolase IB subunit alpha (PAFacetylhydrolase 45 kDa subunit) (PAF-AH 45 kDa subunit) (PAF-AHalpha) (PAFAH alpha) (Lissencephaly-1 protein) (LIS-1); (4641:) Platelet-activating factor acetylhydrolase IB subunit beta (PAFacetylhydrolase 30 kDa subunit) (PAF-AH 30 kDa subunit) (PAF-AHsubunit beta) (PAFAH subunit beta); (4642:) Platelet-activating factor acetylhydrolase IB subunit gamma (PAFacetylhydrolase 29 kDa subunit) (PAF-AH 29 kDa subunit) (PAF-AHsubunit gamma) (PAFAH subunit gamma); (4643:) platelet-activating factor

acetylhydrolase, isoform Ib, alphasubunit (45kD) [Homo sapiens]; (4644:) Platelet-activating factor receptor (PAF-R); (4645:) Platelet-Derived Growth Factor Receptor (PDGFR); (4646:) platelet-derived growth factor receptor beta precursor [Homosapiens]; (4647:) Platelet-derived growth factor-D (PDGF-D); (4648:) platelet-type phosphofructokinase [Homo sapiens]; (4649:) Plexin-A3 precursor (Plexin-4) (Semaphorin receptor SEX); (4650:) Plexin-A4 precursor; (4651:) Plexin-B1 precursor (Semaphorin receptor SEP); (4652:) Plexin-B2 precursor (MM1); (4653:) Plexin-B3 precursor; (4654:) Plexin-D1 precursor; (4655:) PMS1 nirs variant 1 [Homo sapiens]; (4656:) PMS1 nirs variant 2 [Homo sapiens]; (4657:) PMS1 nirs variant 3 [Homo sapiens]; (4658:) PMS1 nirs variant 5 [Homo sapiens]; (4659:) PMS1 nirs variant 6 [Homo sapiens]; (4660:) PMS1 nirs variant 7 [Homo sapiens]; (4661:) PMS1 nirs variant 8 [Homo sapiens]; (4662:) PMS1 nirs variant 9 [Homo sapiens]; (4663:) PMS1 postmeiotic segregation increased 1 (S. cerevisiae) [Homosapiens]; (4664:) PMS1 protein [Homo sapiens]; (4665:) PMS1 protein homolog 1 (DNA mismatch repair protein PMS1); (4666:) PMS1 protein homolog 2 (DNA mismatch repair protein PMS2); (4667:) PMS2 gene; (4668:) PMS2 postmeiotic segregation increased 2 (S. cerevisiae) [Homosapiens]; (4669:) PMS2 postmeiotic segregation increased 2 isoform a [Homo sapiens]; (4670:) PMS2 protein [Homo sapiens]; (4671:) PMS2-C terminal -like [Homo sapiens]; (4672:) PMS2CL protein [Homo sapiens]; (4673:) PMS2L14 [Homo sapiens]; (4674:) PMS2L15 [Homo sapiens]; (4675:) PMS2L16 [Homo sapiens]; (4676:) PMS2L5 protein [Homo sapiens]; (4677:) PMS7 [Homo sapiens]; (4678:) Poliovirus receptor precursor (Nectin-like protein 5) (Necl-5)(CD155 antigen); (4679:) poliovirus receptor-related 4 [Homo sapiens]; (4680:) Poliovirus receptor-related protein 1 precursor (Herpes virus entrymediator C) (HveC) (Nectin-1) (Herpesvirus Ig-like receptor) (HIgR)(CD111 antigen); (4681:) Poliovirus receptor-related protein 2 precursor (Herpes virus entrymediator B) (HveB) (Nectin-2) (CD112 antigen); (4682:) Polo-Like Kinase (Plk); (4683:) polo-like kinase [Homo sapiens]; (4684:) Polo-Like Kinase 1 (Plk1); (4685:) POLS protein [Homo sapiens]; (4686:) poly (ADP-ribose) glycohydrolase [Homo sapiens]; (4687:) poly (ADP-ribose) polymerase family, member 1 [Homo sapiens]; (4688:) poly (ADP-ribose) polymerase family, member 10 [Homo sapiens]; (4689:) Poly [ADP-ribose] polymerase 1 (PARP-1) (ADPRT) (NAD(+)ADP-ribosyltransferase 1) (Poly[ADP-ribose] synthetase 1); (4690:) Poly(A) polymerase gamma (PAP gamma) (Polynucleotideadenylyltransferase gamma) (SRP RNA 3' adenylating enzyme)(Neo-poly(A) polymerase) (Neo-PAP); (4691:) poly(A) polymerase gamma

[Homo sapiens]; (4692:) Poly(A)-specific ribonuclease PARN (Polyadenylate-specificribonuclease) (Deadenylating nuclease) (Deadenylation nuclease); (4693:) Poly(ADP-Ribose) Glycohydrolase (PARG); (4694:) Poly(ADP-ribose) polymerase (PARP); (4695:) Poly(ADP-ribose) polymerase-1 (PARP-1); (4696:) Poly(ADP-ribose) polymerase-2 (PARP-2); (4697:) poly(rC) binding protein 1 [Homo sapiens]; (4698:) polyamine oxidase isoform 1 [Homo sapiens]; (4699:) polyamine oxidase isoform 2 [Homo sapiens]; (4700:) polyamine oxidase isoform 3 [Homo sapiens]; (4701:) polyamine oxidase isoform 4 [Homo sapiens]; (4702:) Polycystic kidney and hepatic disease 1 precursor (Fibrocystin)(Polyductin) (Tigmin); (4703:) polymerase (DNA directed) kappa [Homo sapiens]; (4704:) polymerase (DNA directed), beta [Homo sapiens]; (4705:) polymerase (DNA directed), delta 2, regulatory subunit [Homosapiens]; (4706:) polymerase (DNA directed), eta [Homo sapiens]; (4707:) polymerase (DNA directed), gamma 2, accessory subunit [Homosapiens]; (4708:) polymerase (DNA directed), lambda [Homo sapiens]; (4709:) polymerase (DNA-directed), alpha [Homo sapiens]; (4710:) polymerase (RNA) III (DNA directed) polypeptide A, 155kDa [Homosapiens]; (4711:) polymerase (RNA) III (DNA directed) polypeptide C (62kD) [Homosapiens]; (4712:) polynucleotide kinase 3'-phosphatase [Homo sapiens]; (4713:) Polypeptide N-acetylgalactosaminyltransferase 1 (Protein-UDPacetylgalactosaminyltransferase 1) (UDP-GalNAc:polypeptideN-acetylgalactosaminyltransferase 1) (Polypeptide GalNActransferase 1) (GalNAc-T1) (pp-GaNTase 1) [Contains:) PolypeptideN-acetylgalactosaminyltransferase 1 soluble form]; (4714:) Polypeptide N-acetylgalactosaminyltransferase 10 (Protein-UDPacetylgalactosaminyltransferase 10) (UDP-GalNAc:polypeptideN-acetylgalactosaminyltransferase 10) (Polypeptide GalNActransferase 10) (GalNAc-T10) (pp-GaNTase 10); (4715:) Polypeptide N-acetylgalactosaminyltransferase 11 (Protein-UDPacetylgalactosaminyltransferase 11) (UDP-GalNAc:polypeptideN-acetylgalactosaminyltransferase 11) (Polypeptide GalNActransferase 11) (GalNAc-T11) (pp-GaNTase 11); (4716:) Polypeptide N-acetylgalactosaminyltransferase 12 (Protein-UDPacetylgalactosaminyltransferase 12) (UDP-GalNAc:polypeptideN-acetylgalactosaminyltransferase 12) (Polypeptide GalNActransferase 12) (GalNAc-T12) (pp-GaNTase 12); (4717:) Polypeptide N-acetylgalactosaminyltransferase 13 (Protein-UDPacetylgalactosaminyltransferase 13) (UDP-GalNAc:polypeptideN-acetylgalactosaminyltransferase 13) (Polypeptide GalNActransferase 13) (GalNAc-T13) (pp-GaNTase 13); (4718:) Polypeptide N-acetylgalactosaminyltransferase 14 (Protein-UDPacetylgalactosaminyltransferase 14) (UDP-GalNAc:polypeptideN-acetylgalactosaminyltransferase 14) (Polypeptide GalNActransferase 14) (GalNAc-

T14) (pp-GaNTase 14); (4719:) Polypeptide N-acetylgalactosaminyltransferase 2 (Protein-UDPacetylgalactosaminyltransferase 2) (UDP-GalNAc:polypeptideN-acetylgalactosaminyltransferase 2) (Polypeptide GalNActransferase 2) (GalNAc-T2) (pp-GaNTase 2) [Contains:) PolypeptideN-acetylgalactosaminyltransferase 2 soluble form]; (4720:) polypeptide N-acetylgalactosaminyltransferase 2 [Homo sapiens]; (4721:) Polypeptide N-acetylgalactosaminyltransferase 3 (Protein-UDPacetylgalactosaminyltransferase 3) (UDP-GalNAc:polypeptideN-acetylgalactosaminyltransferase 3) (Polypeptide GalNActransferase 3) (GalNAc-T3) (pp-GaNTase 3); (4722:) Polypeptide N-acetylgalactosaminyltransferase 4 (Protein-UDPacetylgalactosaminyltransferase 4) (UDP-GalNAc:polypeptideN-acetylgalactosaminyltransferase 4) (Polypeptide GalNActransferase 4) (GalNAc-T4) (pp-GaNTase 4); (4723:) Polypeptide N-acetylgalactosaminyltransferase 6 (Protein-UDPacetylgalactosaminyltransferase 6) (UDP-GalNAc:polypeptideN-acetylgalactosaminyltransferase 6) (Polypeptide GalNActransferase 6) (GalNAc-T6) (pp-GaNTase 6); (4724:) polypeptide N-acetylgalactosaminyltransferase 7 [Homo sapiens]; (4725:) polypeptide N-acetylgalactosaminyltransferase 8 [Homo sapiens]; (4726:) Polypeptide N-acetylgalactosaminyltransferase 9 (Protein-UDPacetylgalactosaminyltransferase 9) (UDP-GalNAc:polypeptideN-acetylgalactosaminyltransferase 9) (Polypeptide GalNActransferase 9) (GalNAc-T9) (pp-GaNTase 9); (4727:) Polypeptide N-acetylgalactosaminyltransferase-like protein 2(Protein-UDP acetylgalactosaminyltransferase-like protein 2)(UDP-GalNAc:polypeptide N-acetylgalactosaminyltransferase-likeprotein 2) (Polypeptide GalNAc transferase-like protein 2)(GalNAc-T-like protein 2) (pp-GaNTase-like protein 2); (4728:) polyserase-2 [Homo sapiens]; (4729:) Polyserase-2 precursor (Polyserine protease 2) (Protease serine36); (4730:) Porcine endogenous retrovirus A receptor 1 precursor (PERV-Areceptor 1) (Protein GPR172A); (4731:) Porcine endogenous retrovirus A receptor 2 precursor (PERV-Areceptor 2) (Protein GPR172B); (4732:) Porimin precursor (Transmembrane protein 123) (Pro-oncosis receptorinducing membrane injury) (Keratinocytes-associated transmembraneprotein 3) (KCT-3); (4733:) Porphobilinogen deaminase (Hydroxymethylbilane synthase) (HMBS)(Pre-uroporphyrinogen synthase) (PBG-D); (4734:) "porphobilinogen deaminase; PBGD [Homo sapiens]."; (4735:) postmeiotic segregation 1 [Homo sapiens]; (4736:) postmeiotic segregation increased 2 nirs variant 2 [Homo sapiens]; (4737:) postmeiotic segregation increased 2 nirs variant 5 [Homo sapiens]; (4738:) postmeiotic segregation increased 2-like 5 [Homo sapiens]; (4739:) postreplication repair protein hRAD18p [Homo sapiens]; (4740:) PP3895

[Homo sapiens]; (4741:) PPP2R5E protein [Homo sapiens]; (4742:) prenyl diphosphate synthase, subunit 1 [Homo sapiens]; (4743:) prenyl protein peptidase RCE1 isoform 1 [Homo sapiens]; (4744:) prenyl protein peptidase RCE1 isoform 2 [Homo sapiens]; (4745:) prenylcysteine lyase [Homo sapiens]; (4746:) prenylcysteine oxidase 1 [Homo sapiens]; (4747:) presenilin 1 [Homo sapiens]; (4748:) presenilin 2 isoform 1 [Homo sapiens]; (4749:) presenilin 2 isoform 2 [Homo sapiens]; (4750:) "Presenilin-1 (PS-1) (Protein S182) [Contains:) Presenilin-1 NTFsubunit; Presenilin-1 CTF subunit; Presenilin-1 CTF12 (PS1-CTF12)]."; (4751:) Presequence protease, mitochondrial precursor (hPreP) (Pitrilysinmetalloproteinase 1) (Metalloprotease 1) (hMP1); (4752:) Presqualene diphosphate phosphatase (Phosphatidic acid phosphatasetype 2 domain-containing protein 2); (4753:) prion protein preproprotein [Homo sapiens]; (4754:) pristanoyl-CoA oxidase [Homo sapiens]; (4755:) Pro oligopeptidase; (4756:) Probable allantoicase (Allantoate amidinohydrolase); (4757:) Probable C->U-editing enzyme APOBEC-2; (4758:) Probable calcium-transporting ATPase KIAA0703; (4759:) Probable DNA dC->dU-editing enzyme APOBEC-3A (Phorbolin-1); (4760:) Probable DNA dC->dU-editing enzyme APOBEC-3B (Phorbolin-1-relatedprotein) (Phorbolin-2/3); (4761:) Probable DNA dC->dU-editing enzyme APOBEC-3C (APOBEC1-like)(Phorbolin I protein); (4762:) Probable DNA dC->dU-editing enzyme APOBEC-3D; (4763:) Probable E3 ubiquitin-protein ligase HECTD2 (HECT domain-containingprotein 2); (4764:) Probable E3 ubiquitin-protein ligase HECTD3 (HECT domain-containingprotein 3); (4765:) Probable G-protein coupled receptor 1; (4766:) Probable G-protein coupled receptor 101; (4767:) Probable G-protein coupled receptor 110 precursor (G-proteincoupled receptor PGR19) (G-protein coupled receptor KPG_012); (4768:) Probable G-protein coupled receptor 111 (G-protein coupled receptorPGR20); (4769:) Probable G-protein coupled receptor 112; (4770:) Probable G-protein coupled receptor 113 precursor (G-proteincoupled receptor PGR23); (4771:) Probable G-protein coupled receptor 114 precursor (G-proteincoupled receptor PGR27); (4772:) Probable G-protein coupled receptor 115 (G-protein coupled receptorPGR18); (4773:) Probable G-protein coupled receptor 116 precursor; (4774:) Probable G-protein coupled receptor 119; (4775:) Probable G-protein coupled receptor 12; (4776:) Probable G-protein coupled receptor 123; (4777:) Probable G-protein coupled receptor 124 precursor (Tumorendothelial marker 5); (4778:) Probable G-protein coupled receptor 125 precursor; (4779:) Probable G-protein coupled receptor 126 precursor; (4780:) Probable G-protein coupled receptor 128 precursor; (4781:) Probable G-protein coupled receptor 132 (G2

accumulation protein); (4782:) Probable G-protein coupled receptor 133 precursor (G-proteincoupled receptor PGR25); (4783:) Probable G-protein coupled receptor 135; (4784:) Probable G-protein coupled receptor 139 (G(q)-coupled orphanreceptor GPRg1) (G-protein-coupled receptor PGR3); (4785:) Probable G-protein coupled receptor 141 (G-protein coupled receptorPGR13); (4786:) Probable G-protein coupled receptor 142 (G-protein coupled receptorPGR2); (4787:) Probable G-protein coupled receptor 144 (G-protein coupled receptorPGR24); (4788:) Probable G-protein coupled receptor 148 (G-protein coupled receptorPGR6) (Brain and testis restricted GPCR); (4789:) Probable G-protein coupled receptor 149 (G-protein coupled receptorPGR10); (4790:) Probable G-protein coupled receptor 150; (4791:) Probable G-protein coupled receptor 151 (G-protein coupled receptorPGR7) (GPCR-2037); (4792:) Probable G-protein coupled receptor 152 (G-protein coupled receptorPGR5); (4793:) Probable G-protein coupled receptor 153 (G-protein coupled receptorPGR1); (4794:) Probable G-protein coupled receptor 156 (GABAB-related G-proteincoupled receptor) (G-protein coupled receptor PGR28); (4795:) Probable G-protein coupled receptor 157; (4796:) Probable G-protein coupled receptor 158 precursor; (4797:) Probable G-protein coupled receptor 160; (4798:) Probable G-protein coupled receptor 161 (G-protein coupled receptorRE2); (4799:) Probable G-protein coupled receptor 162 (Gene-rich cluster gene Aprotein); (4800:) Probable G-protein coupled receptor 171 (G-protein coupled receptorH963); (4801:) Probable G-protein coupled receptor 173 (Super conserved receptorexpressed in brain 3); (4802:) Probable G-protein coupled receptor 174; (4803:) Probable G-protein coupled receptor 176 (HB-954); (4804:) Probable G-protein coupled receptor 179 precursor (ProbableG-protein coupled receptor 158-like 1); (4805:) Probable G-protein coupled receptor 18; (4806:) Probable G-protein coupled receptor 19 (GPR-NGA); (4807:) Probable G-protein coupled receptor 20; (4808:) Probable G-protein coupled receptor 21; (4809:) Probable G-protein coupled receptor 22; (4810:) Probable G-protein coupled receptor 25; (4811:) Probable G-protein coupled receptor 26; (4812:) Probable G-protein coupled receptor 27 (Super conserved receptorexpressed in brain 1); (4813:) Probable G-protein coupled receptor 3 (ACCA orphan receptor); (4814:) Probable G-protein coupled receptor 31; (4815:) Probable G-protein coupled receptor 32; (4816:) Probable G-protein coupled receptor 33; (4817:) Probable G-protein coupled receptor 34; (4818:) Probable G-protein coupled receptor 35; (4819:) Probable G-protein coupled receptor 37 precursor (Endothelin Breceptor-like protein 1) (ETBR-LP-1) (Parkin-associated endothelinreceptor-like receptor) (PAELR); (4820:) Probable G-protein coupled

receptor 39; (4821:) Probable G-protein coupled receptor 4 (G-protein coupled receptor19); (4822:) Probable G-protein coupled receptor 45 (PSP24-alpha) (PSP24-1); (4823:) Probable G-protein coupled receptor 52; (4824:) Probable G-protein coupled receptor 55; (4825:) Probable G-protein coupled receptor 61 (Biogenic aminereceptor-like G-protein coupled receptor); (4826:) Probable G-protein coupled receptor 62 (hGPCR8); (4827:) Probable G-protein coupled receptor 63 (PSP24-beta) (PSP24-2); (4828:) Probable G-protein coupled receptor 75; (4829:) Probable G-protein coupled receptor 78; (4830:) Probable G-protein coupled receptor 81 (G-protein coupled receptor104); (4831:) Probable G-protein coupled receptor 82; (4832:) Probable G-protein coupled receptor 83 precursor (G-protein coupledreceptor 72); (4833:) Probable G-protein coupled receptor 84 (Inflammation-relatedG-protein coupled receptor EX33); (4834:) Probable G-protein coupled receptor 85 (Super conserved receptorexpressed in brain 2); (4835:) Probable G-protein coupled receptor 87 (G-protein coupled receptor95); (4836:) Probable G-protein coupled receptor 88 (Striatum-specific G-proteincoupled receptor); (4837:) Probable G-protein coupled receptor 92; (4838:) Probable G-protein coupled receptor 97 precursor (G-protein coupledreceptor PGR26); (4839:) Probable G-protein-coupled receptor 146 (G-protein coupled receptorPGR8); (4840:) Probable P2Y purinoceptor GPR17 (G protein-coupled receptor 17)(P2Y-like receptor) (R12); (4841:) Probable ubiquitin carboxyl-terminal hydrolase CYLD (Ubiquitinthioesterase CYLD) (Ubiquitin-specific-processing protease CYLD)(Deubiquitinating enzyme CYLD); (4842:) Probable ubiquitin carboxyl-terminal hydrolase FAF-X (Ubiquitinthioesterase FAF-X) (Ubiquitin-specific-processing protease FAF-X)(Deubiquitinating enzyme FAF-X) (Fat facets protein-related,X-linked) (Ubiquitin-specific protease 9, X chromosome); (4843:) Probable ubiquitin carboxyl-terminal hydrolase FAF-Y (Ubiquitinthioesterase FAF-Y) (Ubiquitin-specific-processing protease FAF-Y)(Deubiquitinating enzyme FAF-Y) (Fat facets protein-related,Y-linked) (Ubiquitin-specific protease 9, Y chromosome); (4844:) Probable ubiquitin-conjugating enzyme E2 W (Ubiquitin-proteinligase W) (Ubiquitin carrier protein W); (4845:) procaspase-8 [Homo sapiens]; (4846:) procaspase-8L [Homo sapiens]; (4847:) procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2 isoform aprecursor [Homo sapiens]; (4848:) procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2 isoform bprecursor [Homo sapiens]; (4849:) procollagen-lysine, 2-oxoglutarate 5-dioxygenase 3 precursor [Homosapiens]; (4850:) Procollagen-lysine,2-oxoglutarate 5-dioxygenase 1 precursor (Lysylhydroxylase 1) (LH1); (4851:) Procollagen-lysine,2-oxoglutarate 5-dioxygenase 2 precursor (Lysylhydroxylase 2) (LH2); (4852:)

Progesterone Receptor (PR); (4853:) Progesterone-induced-blocking factor 1; (4854:) Progestin and adipoQ receptor family member 3 (Progestin and adipoQreceptor family member III); (4855:) Progestin and adipoQ receptor family member 4 (Progestin and adipoQreceptor family member IV); (4856:) Progestin and adipoQ receptor family member 6 (Progestin and adipoQreceptor family member VI); (4857:) Progestin and adipoQ receptor family member 9 (Progestin and adipoQreceptor family member IX); (4858:) Programmed Cell Death 1 (PDCD1) Receptor; (4859:) Programmed cell death 1 ligand 1 precursor (Programmed death ligand1) (PD-L1) (PDCD1 ligand 1) (B7 homolog 1) (B7-H1) (CD274 antigen); (4860:) Programmed cell death 1 ligand 2 precursor (Programmed death ligand2) (PD-L2) (PD-1-ligand 2) (PDCD1 ligand 2) (Butyrophilin B7-DC)(B7-DC) (CD273 antigen); (4861:) Prohibitin-2 (B-cell receptor-associated protein BAP37) (Repressorof estrogen receptor activity) (D-prohibitin); (4862:) prohormone convertase 2 [Homo sapiens]; (4863:) prohormone convertase 2, PC2 [human, Peptide, 638 aa]; (4864:) prohormone convertase; (4865:) proinsulin precursor [Homo sapiens]; (4866:) Prokineticin 2 (PK2) Receptor; (4867:) Prokineticin receptor 1 (PK-R1) (G-protein coupled receptor 73)(GPR73a) (G-protein coupled receptor ZAQ); (4868:) Prokineticin receptor 2 (PK-R2) (G-protein coupled receptor 73-like1) (GPR73b) (GPRg2); (4869:) Prolactin receptor precursor (PRL-R); (4870:) Prolactin-releasing peptide receptor (PrRP receptor) (PrRPR)(G-protein coupled receptor 10) (hGR3); (4871:) proliferating cell nuclear antigen [Homo sapiens]; (4872:) Prolyl 4-Hydroxylase; (4873:) prolyl 4-hydroxylase alpha (II) subunit [Homo sapiens]; (4874:) Prolyl 4-hydroxylase alpha-2 subunit precursor (4-PH alpha-2)(Procollagen-proline,2-oxoglutarate-4-dioxygenase alpha-2 subunit); (4875:) prolyl 4-hydroxylase, alpha I subunit isoform 1 precursor [Homosapiens]; (4876:) prolyl 4-hydroxylase, alpha I subunit isoform 2 precursor [Homosapiens]; (4877:) prolyl 4-hydroxylase, alpha II subunit isoform 1 precursor [Homosapiens]; (4878:) prolyl 4-hydroxylase, alpha II subunit isoform 2 precursor [Homosapiens]; (4879:) prolyl 4-hydroxylase, alpha III subunit precursor [Homo sapiens]; (4880:) prolyl 4-hydroxylase, beta subunit [Homo sapiens]; (4881:) Prolyl Endopeptidase (PEP); (4882:) prolyl endopeptidase [Homo sapiens]; (4883:) prolylcarboxypeptidase isoform 1 preproprotein [Homo sapiens]; (4884:) prolylcarboxypeptidase isoform 2 preproprotein [Homo sapiens]; (4885:) prolylcarboxypeptidase; (4886:) pro-matrix metalloproteinase-3 - human (fragment); (4887:) proMch6; (4888:) Promyelocytic Leukemia/Retinoic Acid Receptor Alpha (PML/RAR) Protein; (4889:) Properdin precursor (Factor P); (4890:) "propionyl CoA carboxylase alpha subunit; PCCA

[Homo sapiens]."; (4891:) propionyl Coenzyme A carboxylase, alpha polypeptide [Homo sapiens]; (4892:) propionyl-CoA carboxylase [Homo sapiens]; (4893:) Propionyl-CoA carboxylase alpha chain, mitochondrial precursor(PCCase subunit alpha) (Propanoyl-CoA:carbon dioxide ligase subunitalpha); (4894:) propionyl-CoA carboxylase alpha polypeptide precursor [Homosapiens]; (4895:) propionyl-CoA carboxylase alpha subunit [Homo sapiens]; (4896:) Propionyl-CoA carboxylase beta chain, mitochondrial precursor(PCCase subunit beta) (Propanoyl-CoA:carbon dioxide ligase subunitbeta); (4897:) propionyl-CoA carboxylase; (4898:) propionyl-Coenzyme A carboxylase, alpha polypeptide precursor [Homosapiens]; (4899:) proprotein convertase subtilisin/kexin type 1 preproprotein [Homosapiens]; (4900:) proprotein convertase subtilisin/kexin type 2 [Homo sapiens]; (4901:) proprotein convertase subtilisin/kexin type 5 preproprotein [Homosapiens]; (4902:) Proprotein convertase subtilisin/kexin type 6 precursor (Pairedbasic amino acid cleaving enzyme 4) (Subtilisin/kexin-like proteasePACE4) (Subtilisin-like proprotein convertase 4) (SPC4); (4903:) Proprotein convertase subtilisin/kexin type 7 precursor (Proproteinconvertase PC7) (Subtilisin/kexin-like protease PC7) (Prohormoneconvertase PC7) (PC8) (hPC8) (Lymphoma proprotein convertase); (4904:) proprotein convertase subtilisin/kexin type 7 preproprotein [Homosapiens]; (4905:) Proprotein convertase subtilisin/kexin type 9 precursor (Proproteinconvertase PC9) (Subtilisin/kexin-like protease PC9) (Neuralapoptosis-regulated convertase 1) (NARC-1); (4906:) prosaposin isoform a preproprotein [Homo sapiens]; (4907:) prosaposin isoform b preproprotein [Homo sapiens]; (4908:) prosaposin isoform c preproprotein [Homo sapiens]; (4909:) Prostacyclin receptor (Prostanoid IP receptor) (PGI receptor)(Prostaglandin I2 receptor); (4910:) Prostaglandin D2 (PGD2) Receptor; (4911:) Prostaglandin D2 receptor (Prostanoid DP receptor) (PGD receptor); (4912:) Prostaglandin E synthase (Microsomal glutathione S-transferase1-like 1) (MGST1-L1) (p53-induced apoptosis protein 12); (4913:) prostaglandin E synthase [Homo sapiens]; (4914:) Prostaglandin E synthase 2 (Microsomal prostaglandin E synthase 2)(mPGES-2) [Contains:) Prostaglandin E synthase 2 truncated form]; (4915:) Prostaglandin E1 (PGE1) Receptor; (4916:) prostaglandin E2 receptor EP3-chain - human; (4917:) Prostaglandin E2 receptor, EP1 subtype (Prostanoid EP1 receptor)(PGE receptor, EP1 subtype); (4918:) Prostaglandin E2 receptor, EP2 subtype (Prostanoid EP2 receptor)(PGE receptor, EP2 subtype); (4919:) Prostaglandin E2 receptor, EP3 subtype (Prostanoid EP3 receptor)(PGE receptor, EP3 subtype) (PGE2-R); (4920:) Prostaglandin E2 receptor, EP4 subtype (Prostanoid EP4 receptor)(PGE receptor, EP4 subtype);

(4921:) Prostaglandin F2 alpha (PGF2 alpha) Receptor; (4922:) Prostaglandin F2-alpha receptor (Prostanoid FP receptor) (PGFreceptor) (PGF2 alpha receptor); (4923:) Prostaglandin G/H synthase 1 precursor (Cyclooxygenase-1) (COX-1)(Prostaglandin-endoperoxide synthase 1) (Prostaglandin H2 synthase1) (PGH synthase 1) (PGHS-1) (PHS 1); (4924:) Prostaglandin G/H synthase 2 precursor (Cyclooxygenase-2) (COX-2)(Prostaglandin-endoperoxide synthase 2) (Prostaglandin H2 synthase2) (PGH synthase 2) (PGHS-2) (PHS II); (4925:) Prostaglandin I2 (PGI2) Receptor; (4926:) prostaglandin I2 (prostacyclin) synthase [Homo sapiens]; (4927:) prostaglandin-D synthase [Homo sapiens]; (4928:) prostaglandin-endoperoxide synthase 1 isoform 1 precursor [Homosapiens]; (4929:) prostaglandin-endoperoxide synthase 1 isoform 2 precursor [Homosapiens]; (4930:) prostaglandin-endoperoxide synthase 2 precursor [Homo sapiens]; (4931:) prostaglandin-endoperoxide synthase-1 [Homo sapiens]; (4932:) Prostasin; (4933:) prostasin preproprotein [Homo sapiens]; (4934:) Prostate-Specific Membrane Antigen (PSMA); (4935:) prostatic acid phosphatase precursor [Homo sapiens]; (4936:) protease, serine, 1 preproprotein [Homo sapiens]; (4937:) protease, serine, 2 preproprotein [Homo sapiens]; (4938:) protease, serine, 22 [Homo sapiens]; (4939:) protease, serine, 36 [Homo sapiens]; (4940:) Protease-Activated Receptor 1 (PAR1); (4941:) Proteasome; (4942:) proteasome 26S ATPase subunit 1 [Homo sapiens]; (4943:) proteasome 26S ATPase subunit 2 [Homo sapiens]; (4944:) proteasome 26S ATPase subunit 3 [Homo sapiens]; (4945:) proteasome 26S ATPase subunit 4 isoform 1 [Homo sapiens]; (4946:) proteasome 26S ATPase subunit 4 isoform 2 [Homo sapiens]; (4947:) proteasome 26S ATPase subunit 5 [Homo sapiens]; (4948:) proteasome 26S ATPase subunit 6 [Homo sapiens]; (4949:) proteasome 26S non-ATPase subunit 1 [Homo sapiens]; (4950:) proteasome 26S non-ATPase subunit 10 isform 2 [Homo sapiens]; (4951:) proteasome 26S non-ATPase subunit 10 isoform 1 [Homo sapiens]; (4952:) proteasome 26S non-ATPase subunit 11 [Homo sapiens]; (4953:) proteasome 26S non-ATPase subunit 12 [Homo sapiens]; (4954:) proteasome 26S non-ATPase subunit 13 isoform 1 [Homo sapiens]; (4955:) proteasome 26S non-ATPase subunit 13 isoform 2 [Homo sapiens]; (4956:) proteasome 26S non-ATPase subunit 2 [Homo sapiens]; (4957:) proteasome 26S non-ATPase subunit 3 [Homo sapiens]; (4958:) proteasome 26S non-ATPase subunit 4 isoform 1 [Homo sapiens]; (4959:) proteasome 26S non-ATPase subunit 4 isoform 2 [Homo sapiens]; (4960:) proteasome 26S non-ATPase subunit 5 [Homo sapiens]; (4961:) proteasome 26S non-ATPase subunit 7 [Homo sapiens]; (4962:) proteasome 26S non-ATPase

subunit 8 [Homo sapiens]; (4963:) proteasome 26S non-ATPase subunit 9 [Homo sapiens]; (4964:) proteasome activator hPA28 suunit beta [Homo sapiens]; (4965:) proteasome activator subunit 1 isoform 1 [Homo sapiens]; (4966:) proteasome activator subunit 1 isoform 2 [Homo sapiens]; (4967:) proteasome activator subunit 2 [Homo sapiens]; (4968:) proteasome activator subunit 3 isoform 1 [Homo sapiens]; (4969:) proteasome activator subunit 3 isoform 2 [Homo sapiens]; (4970:) proteasome alpha 1 subunit isoform 1 [Homo sapiens]; (4971:) proteasome alpha 1 subunit isoform 2 [Homo sapiens]; (4972:) proteasome alpha 2 subunit [Homo sapiens]; (4973:) proteasome alpha 3 subunit isoform 1 [Homo sapiens]; (4974:) proteasome alpha 3 subunit isoform 2 [Homo sapiens]; (4975:) proteasome alpha 4 subunit [Homo sapiens]; (4976:) proteasome alpha 5 subunit [Homo sapiens]; (4977:) proteasome alpha 6 subunit [Homo sapiens]; (4978:) proteasome alpha 7 subunit [Homo sapiens]; (4979:) proteasome beta 1 subunit [Homo sapiens]; (4980:) proteasome beta 10 subunit proprotein [Homo sapiens]; (4981:) proteasome beta 2 subunit [Homo sapiens]; (4982:) proteasome beta 3 subunit [Homo sapiens]; (4983:) proteasome beta 4 subunit [Homo sapiens]; (4984:) proteasome beta 5 subunit [Homo sapiens]; (4985:) proteasome beta 6 subunit [Homo sapiens]; (4986:) proteasome beta 7 subunit proprotein [Homo sapiens]; (4987:) proteasome beta 8 subunit isoform E1 proprotein [Homo sapiens]; (4988:) proteasome beta 8 subunit isoform E2 proprotein [Homo sapiens]; (4989:) proteasome beta 9 subunit isoform 1 proprotein [Homo sapiens]; (4990:) proteasome beta 9 subunit isoform 2 proprotein [Homo sapiens]; (4991:) proteasome inhibitor subunit 1 isoform 1 [Homo sapiens]; (4992:) proteasome inhibitor subunit 1 isoform 2 [Homo sapiens]; (4993:) Proteasome subunit alpha type 1 (Proteasome component C2)(Macropain subunit C2) (Multicatalytic endopeptidase complexsubunit C2) (Proteasome nu chain) (30 kDa prosomal protein)(PROS-30); (4994:) Proteasome subunit alpha type 2 (Proteasome component C3)(Macropain subunit C3) (Multicatalytic endopeptidase complexsubunit C3); (4995:) Proteasome subunit alpha type 3 (Proteasome component C8)(Macropain subunit C8) (Multicatalytic endopeptidase complexsubunit C8); (4996:) Proteasome subunit alpha type 4 (Proteasome component C9)(Macropain subunit C9) (Multicatalytic endopeptidase complexsubunit C9) (Proteasome subunit L); (4997:) Proteasome subunit beta type 1 (Proteasome component C5) (Macropainsubunit C5) (Multicatalytic endopeptidase complex subunit C5)(Proteasome gamma chain); (4998:) Proteasome subunit beta type 2 (Proteasome component C7-I)(Macropain subunit C7-I) (Multicatalytic endopeptidase complexsubunit C7-I); (4999:) Proteasome subunit beta type 3

(Proteasome theta chain) (Proteasomechain 13) (Proteasome component C10-II); (5000:) Proteasome subunit beta type 4 precursor (Proteasome beta chain)(Macropain beta chain) (Multicatalytic endopeptidase complex betachain) (Proteasome chain 3) (HSN3) (HsBPROS26); (5001:) proteasome subunit C2 [Homo sapiens]; (5002:) proteasome subunit C3 [Homo sapiens]; (5003:) proteasome subunit C5 [Homo sapiens]; (5004:) proteasome subunit C8 [Homo sapiens]; (5005:) proteasome subunit C9 [Homo sapiens]; (5006:) proteasome subunit HsC10-II [Homo sapiens]; (5007:) proteasome subunit HsC7-I [Homo sapiens]; (5008:) proteasome subunit HsN3 [Homo sapiens]; (5009:) proteasome subunit p40 / Mov34 protein [Homo sapiens]; (5010:) proteasome subunit X [Homo sapiens]; (5011:) proteasome subunit Y [Homo sapiens]; (5012:) proteasome:SUBUNIT=HsC10-II; (5013:) proteasome:SUBUNIT=HsC7-I; (5014:) proteasome:SUBUNIT=HsN3; (5015:) protective protein for beta-galactosidase [Homo sapiens]; (5016:) Protein arginine N-methyltransferase 1 (Interferon receptor 1-boundprotein 4); (5017:) Protein arginine N-methyltransferase 3 (Heterogeneous nuclearribonucleoprotein methyltransferase-like protein 3); (5018:) Protein arginine N-methyltransferase 6 (Heterogeneous nuclearribonucleoprotein methyltransferase-like protein 6); (5019:) Protein ariadne-1 homolog (ARI-1) (Ubiquitin-conjugating enzymeE2-binding protein 1) (UbcH7-binding protein) (UbcM4-interactingprotein) (HHARI) (H7-AP2) (MOP-6); (5020:) protein disulfide isomerase-associated 3 precursor [Homo sapiens]; (5021:) protein disulfide isomerase-associated 4 [Homo sapiens]; (5022:) protein disulfide isomerase-related protein; (5023:) Protein disulfide-isomerase A4 precursor (Protein ERp-72) (ERp72); (5024:) Protein disulfide-isomerase TXNDC10 precursor (Thioredoxindomain-containing protein 10) (Thioredoxin-related transmembraneprotein 3); (5025:) Protein FAM125A (CIN85/CD2AP family-binding protein); (5026:) protein kinase (EC 2.7.1.37), cAMP-dependent, type I-betaregulatory chain - human; (5027:) Protein Kinase A (PKA); (5028:) Protein Kinase B (PKB); (5029:) Protein Kinase B (PKB); (5030:) protein kinase C (EC 2.7.1.-) beta-I - human; (5031:) Protein Kinase C (PKC); (5032:) Protein kinase C alpha type (PKC-alpha) (PKC-A); (5033:) Protein kinase C beta type (PKC-beta) (PKC-B); (5034:) Protein kinase C delta type (nPKC-delta); (5035:) Protein kinase C epsilon type (nPKC-epsilon); (5036:) Protein kinase C eta type (nPKC-eta) (PKC-L); (5037:) Protein kinase C gamma type (PKC-gamma); (5038:) Protein kinase C iota type (nPKC-iota) (Atypical protein kinaseC-lambda/iota) (aPKC-lambda/iota) (PRKC-lambda/iota); (5039:) protein kinase C substrate 80K-H isoform 1 [Homo sapiens]; (5040:) protein kinase C substrate 80K-H isoform 2

[Homo sapiens]; (5041:) Protein kinase C theta type (nPKC-theta); (5042:) Protein kinase C zeta type (nPKC-zeta); (5043:) protein kinase C, alpha [Homo sapiens]; (5044:) protein kinase C, delta [Homo sapiens]; (5045:) protein kinase C, epsilon [Homo sapiens]; (5046:) protein kinase C, gamma [Homo sapiens]; (5047:) Protein Kinase C-alpha (PKC-alpha); (5048:) Protein Kinase C-beta (PKC-beta); (5049:) Protein Kinase C-delta (PKC-delta); (5050:) protein kinase CHK2 isoform a [Homo sapiens]; (5051:) protein kinase CHK2 isoform b [Homo sapiens]; (5052:) protein kinase CHK2 isoform c [Homo sapiens]; (5053:) protein kinase, cGMP-dependent, type I [Homo sapiens]; (5054:) protein kinase, DNA-activated, catalytic polypeptide [Homosapiens]; (5055:) Protein Kinase-C Like 2 (PRKCL2); (5056:) Protein LMBR1L (Lipocalin-1-interacting membrane receptor)(Lipocalin-interacting membrane receptor) (Limb region 1 proteinhomolog-like); (5057:) Protein MTO1 homolog, mitochondrial precursor; (5058:) Protein N-terminal asparagine amidohydrolase (Protein NH2-terminalasparagine deamidase) (N-terminal Asn amidase) (NTN-amidase) (PNAD)(Protein NH2-terminal asparagine amidohydrolase) (PNAA); (5059:) protein O-fucosyltransferase 1 isoform 1 precursor [Homo sapiens]; (5060:) protein O-fucosyltransferase 1 isoform 2 precursor [Homo sapiens]; (5061:) Protein O-mannosyl-transferase 1(Dolichyl-phosphate-mannose--protein mannosyltransferase 1); (5062:) Protein O-mannosyl-transferase 2(Dolichyl-phosphate-mannose--protein mannosyltransferase 2); (5063:) Protein patched homolog 1 (PTC1) (PTC); (5064:) Protein patched homolog 2 (PTC2); (5065:) protein phosphatase 1, catalytic subunit, alpha isoform 1 [Homosapiens]; (5066:) protein phosphatase 1, catalytic subunit, alpha isoform 2 [Homosapiens]; (5067:) protein phosphatase 1, catalytic subunit, alpha isoform 3 [Homosapiens]; (5068:) protein phosphatase 1, catalytic subunit, gamma isoform [Homosapiens]; (5069:) protein phosphatase 1G [Homo sapiens]; (5070:) protein phosphatase 1J (PP2C domain containing) [Homo sapiens]; (5071:) protein phosphatase 2, catalytic subunit, alpha isoform [Homosapiens]; (5072:) protein phosphatase 2, catalytic subunit, beta isoform [Homosapiens]; (5073:) protein phosphatase 2, regulatory subunit B (B56), alpha isoform[Homo sapiens]; (5074:) protein phosphatase 2, regulatory subunit B", alpha isoform 1[Homo sapiens]; (5075:) protein phosphatase 2, regulatory subunit B", alpha isoform 2[Homo sapiens]; (5076:) protein phosphatase 2, regulatory subunit B", beta isoform 1 [Homosapiens]; (5077:) protein phosphatase 2, regulatory subunit B", beta isoform 2 [Homosapiens]; (5078:) protein phosphatase 2A, regulatory subunit B' isoform a [Homosapiens]; (5079:) protein phosphatase 2A, regulatory subunit B' isoform b [Homosapiens]; (5080:) protein

phosphatase 2A, regulatory subunit B' isoform d [Homosapiens]; (5081:) Protein phosphatase 2C isoform alpha (PP2C-alpha) (IA) (Proteinphosphatase 1A); (5082:) Protein phosphatase 2C isoform beta (PP2C-beta); (5083:) Protein preY, mitochondrial precursor; (5084:) Protein Tyrosine Phosphatase 1B (PTP1B); (5085:) Protein tyrosine phosphatase type IVA protein 1 (Protein-tyrosinephosphatase 4a1) (Protein-tyrosine phosphatase of regeneratingliver 1) (PRL-1) (PTP(CAAXI)); (5086:) Protein tyrosine phosphatase type IVA protein 2 (Protein-tyrosinephosphatase 4a2) (Protein-tyrosine phosphatase of regeneratingliver 2) (PRL-2) (PTP(CAAXII)) (HU-PP-1) (OV-1); (5087:) Protein tyrosine phosphatase type IVA protein 3 (Protein-tyrosinephosphatase 4a3) (Protein-tyrosine phosphatase of regeneratingliver 3) (PRL-3) (PRL-R); (5088:) protein tyrosine phosphatase type IVA, member 1 [Homo sapiens]; (5089:) protein tyrosine phosphatase, non-receptor type 22 (lymphoid)isoform 1 [Homo sapiens]; (5090:) protein tyrosine phosphatase, non-receptor type 22 (lymphoid)isoform 2 [Homo sapiens]; (5091:) protein tyrosine phosphatase, receptor type, N precursor [Homosapiens]; (5092:) protein X [Homo sapiens]; (5093:) protein Z; (5094:) Protein-arginine deiminase type-3 (Protein-arginine deiminase typeIII) (Peptidylarginine deiminase III); (5095:) Protein-arginine deiminase type-4 (Protein-arginine deiminase typeIV) (Peptidylarginine deiminase IV) (HL-60 PAD); (5096:) proteinase 3 (serine proteinase, neutrophil, Wegener granulomatosisautoantigen) [Homo sapiens]; (5097:) Proteinase Activated Receptor-2 (PAR-2); (5098:) Proteinase-activated receptor 1 precursor (PAR-1) (Thrombinreceptor) (Coagulation factor II receptor); (5099:) Proteinase-activated receptor 2 precursor (PAR-2) (Thrombinreceptor-like 1) (Coagulation factor II receptor-like 1) (G-proteincoupled receptor 11); (5100:) Proteinase-activated receptor 3 precursor (PAR-3) (Thrombinreceptor-like 2) (Coagulation factor II receptor-like 2); (5101:) Proteinase-activated receptor 4 precursor (PAR-4) (Thrombinreceptor-like 3) (Coagulation factor II receptor-like 3); (5102:) Protein-glutamine gamma-glutamyltransferase 5 (Transglutaminase-5)(TGase 5) (Transglutaminase X) (TGase X) (TGX) (TG(X)); (5103:) "Protein-glutamine gamma-glutamyltransferase E precursor (TGase E)(TGE) (TG(E)) (Transglutaminase-3) [Contains:) Protein-glutaminegamma-glutamyltransferase E 50 kDa non-catalytic chain;Protein-glutamine gamma-glutamyltransferase E 27 kDa catalyticchain]."; (5104:) Protein-glutamine gamma-glutamyltransferase K (Transglutaminase K)(TGase K) (TGK) (TG(K)) (Transglutaminase-1) (Epidermal TGase); (5105:) protein-L-isoaspartate (D-aspartate) O-methyltransferase [Homosapiens]; (5106:) protein-O-mannosyltransferase 1 isoform a [Homo sapiens]; (5107:) protein-O-

mannosyltransferase 1 isoform b [Homo sapiens]; (5108:) protein-O-mannosyltransferase 1 isoform c [Homo sapiens]; (5109:) protein-tyrosine kinase (EC 2.7.1.112), receptor type tie precursor- human; (5110:) Protein-tyrosine sulfotransferase 1 (Tyrosylproteinsulfotransferase-1) (TPST-1); (5111:) protein-tyrosine-phosphatase (EC 3.1.3.48), receptor type Hprecursor - human; (5112:) protein-tyrosine-phosphatase (EC 3.1.3.48), receptor type Oprecursor - human; (5113:) "Prothrombin precursor (Coagulation factor II) [Contains:) Activationpeptide fragment 1; Activation peptide fragment 2; Thrombin lightchain; Thrombin heavy chain]."; (5114:) protooncogene protein 1 [Homo sapiens]; (5115:) Proto-oncogene tyrosine-protein kinase ABL1 (p150) (c-ABL) (Abelsonmurine leukemia viral oncogene homolog 1); (5116:) Proto-oncogene tyrosine-protein kinase MER precursor (C-mer)(Receptor tyrosine kinase MerTK); (5117:) Proto-oncogene tyrosine-protein kinase ROS precursor (c-ros-1); (5118:) Protoporphyrinogen oxidase (PPO); (5119:) PRTD-NY3 [Homo sapiens]; (5120:) P-Selectin Activator; (5121:) Psychosine receptor (G-protein coupled receptor 65) (T celldeath-associated protein 8); (5122:) pterin carbinolamine dehydratase [Homo sapiens]; (5123:) pterin-4 alpha-carbinolamine dehydratase precursor [Homo sapiens]; (5124:) Pterin-4 alpha-carbinolamine dehydratase/dimerization cofactor ofhepatocyte nuclear factor 1 alpha (TCF1) [Homo sapiens]; (5125:) Pterin-4 alpha-carbinolamine dehydratase/dimerization cofactor ofhepatocyte nuclear factor 1 alpha (TCF1) 2 [Homo sapiens]; (5126:) pterin-4a-carbinolamine dehydratase; (5127:) Pterin-4-alpha-carbinolamine dehydratase (PHS)(4-alpha-hydroxy-tetrahydropterin dehydratase) (Phenylalaninehydroxylase-stimulating protein) (Pterin carbinolamine dehydratase)(PCD) (Dimerization cofactor of hepatocyte nuclear factor 1-alpha)(Dimerization cofactor of HNF1) (DCoH); (5128:) Pterin-4-alpha-carbinolamine dehydratase 2 (PHS 2)(4-alpha-hydroxy-tetrahydropterin dehydratase 2) (DcoH-like proteinDCoHm) (Dimerization cofactor of hepatocyte nuclear factor 1 frommuscle) (HNF1-alpha dimerization cofactor); (5129:) PTK2 protein tyrosine kinase 2 isoform a [Homo sapiens]; (5130:) PTK2 protein tyrosine kinase 2 isoform b [Homo sapiens]; (5131:) P-Type Calcium Channel Blocker; (5132:) Purine Nucleoside Phosphorylase (PNP); (5133:) purine nucleoside phosphorylase [Homo sapiens]; (5134:) putative 1-aminocyclopropane-1-carboxylate synthase [Homo sapiens]; (5135:) putative acyl-CoA dehydrogenase [Homo sapiens]; (5136:) putative b,b-carotene-9',10'-dioxygenase [Homo sapiens]; (5137:) Putative C->U-editing enzyme APOBEC-4 (Apolipoprotein BmRNA-editing enzyme catalytic polypeptide-like 4); (5138:) putative carotene dioxygenase [Homo sapiens]; (5139:) putative deubiquitinazing

enzyme [Homo sapiens]; (5140:) Putative G-protein coupled receptor 42; (5141:) Putative G-protein coupled receptor 44 (Chemoattractantreceptor-homologous molecule expressed on Th2 cells) (CD294antigen); (5142:) "putative non-ribosomal peptide synthetase NRPS1098; hNRPS1098 [Homosapiens]."; (5143:) putative non-ribosomal peptide synthetase NRPS998 [Homo sapiens]; (5144:) Putative P2Y purinoceptor 10 (P2Y10) (P2Y-like receptor); (5145:) putative peroxisomal antioxidant enzyme [Homo sapiens]; (5146:) putative protein O-mannosyltransferase [Homo sapiens]; (5147:) putative pyroglutamyl-peptidase I [Homo sapiens]; (5148:) Putative Taste receptor type 2 member 12 (T2R12) (Taste receptortype 2 member 26) (T2R26); (5149:) putative ubiquitin-conjugating enzyme E2 variant [Homo sapiens]; (5150:) pVHL-interacting deubiquitinating enzyme 1 type I [Homo sapiens]; (5151:) pVHL-interacting deubiquitinating enzyme 1 type II [Homo sapiens]; (5152:) pVHL-interacting deubiquitinating enzyme 2 [Homo sapiens]; (5153:) Pyridoxal kinase (Pyridoxine kinase); (5154:) pyridoxal kinase [Homo sapiens]; (5155:) Pyridoxal phosphate phosphatase (PLP phosphatase); (5156:) Pyridoxal phosphate phosphatase PHOSPHO2; (5157:) pyridoxine 5'-phosphate oxidase [Homo sapiens]; (5158:) pyroglutamyl-peptidase I [Homo sapiens]; (5159:) pyrophosphatase 1 [Homo sapiens]; (5160:) pyrroline 5-carboxylate synthetase [Homo sapiens]; (5161:) pyrroline-5-carboxylate reductase 1 isoform 1 [Homo sapiens]; (5162:) pyrroline-5-carboxylate reductase 1 isoform 2 [Homo sapiens]; (5163:) pyrroline-5-carboxylate synthase [Homo sapiens]; (5164:) pyrroline-5-carboxylate synthase long form [Homo sapiens]; (5165:) pyrroline-5-carboxylate synthetase isoform 1 [Homo sapiens]; (5166:) pyrroline-5-carboxylate synthetase isoform 2 [Homo sapiens]; (5167:) Pyruvate carboxylase [Homo sapiens]; (5168:) pyruvate carboxylase precursor [Homo sapiens]; (5169:) pyruvate carboxylase precursor; (5170:) Pyruvate carboxylase, mitochondrial precursor (Pyruvic carboxylase)(PCB); (5171:) pyruvate carboxylase; (5172:) "pyruvate carboxylase; pyruvate:carbon dioxide ligase [Homosapiens]."; (5173:) pyruvate dehydrogenase (lipoamide) alpha 1 [Homo sapiens]; (5174:) Pyruvate Dehydrogenase (PDH) Kinase; (5175:) pyruvate dehydrogenase complex protein X subunit precursor [Homosapiens]; (5176:) pyruvate dehydrogenase complex, component X [Homo sapiens]; (5177:) Pyruvate dehydrogenase E1 component alpha subunit, somatic form,mitochondrial precursor (PDHE1-A type I); (5178:) Pyruvate dehydrogenase E1 component alpha subunit, testis-specificform, mitochondrial precursor (PDHE1-A type II); (5179:) Pyruvate dehydrogenase E1 component subunit beta, mitochondrialprecursor (PDHE1-B); (5180:) Pyruvate Dehydrogenase Kinase 2

(PDHK2); (5181:) Pyruvate dehydrogenase protein X component, mitochondrial precursor(Dihydrolipoamide dehydrogenase-binding protein of pyruvatedehydrogenase complex) (Lipoyl-containing pyruvate dehydrogenasecomplex component X) (E3-binding protein) (E3BP) (proX); (5182:) pyruvate kinase (EC 2.7.1.40), muscle splice form M1 - human; (5183:) pyruvate kinase [Homo sapiens]; (5184:) pyruvate kinase 3 isoform 1 [Homo sapiens]; (5185:) pyruvate kinase 3 isoform 1 variant [Homo sapiens]; (5186:) pyruvate kinase 3 isoform 2 [Homo sapiens]; (5187:) Pyruvate kinase isozymes M1/M2 (Pyruvate kinase muscle isozyme)(Pyruvate kinase 2/3) (Cytosolic thyroid hormone-binding protein)(CTHBP) (THBP1); (5188:) Pyruvate kinase isozymes R/L (R-type/L-type pyruvate kinase) (Redcell/liver pyruvate kinase) (Pyruvate kinase 1); (5189:) pyruvate kinase L [Homo sapiens]; (5190:) pyruvate kinase M2 [Homo sapiens]; (5191:) pyruvate kinase PK-L isoenzyme [Homo sapiens]; (5192:) pyruvate kinase PK-R isoenzyme [Homo sapiens]; (5193:) Pyruvate kinase, liver and RBC [Homo sapiens]; (5194:) pyruvate kinase, liver and RBC isoform 1 [Homo sapiens]; (5195:) pyruvate kinase, liver and RBC isoform 2 [Homo sapiens]; (5196:) Pyruvate kinase, muscle [Homo sapiens]; (5197:) pyruvate kinase; (5198:) carbon-dioxide ligase (ADP-forming); (5199:) Pyruvate:Ferredoxin Oxidoreductase (PFOR); (5200:) QTRT1 protein [Homo sapiens]; (5201:) QTRTD1 protein [Homo sapiens]; (5202:) Queuine tRNA-ribosyltransferase (tRNA-guanine transglycosylase)(Guanine insertion enzyme); (5203:) quinoid dihydropteridine reductase [Homo sapiens]; (5204:) quinolinate phosphoribosyltransferase [Homo sapiens]; (5205:) rabaptin, RAB GTPase binding effector protein 1 [Homo sapiens]; (5206:) Rac GTPase activating protein 1 [Homo sapiens]; (5207:) RAD18 [Homo sapiens]; (5208:) RAD51 homolog protein isoform 1 [Homo sapiens]; (5209:) RAD51 homolog protein isoform 2 [Homo sapiens]; (5210:) RAD6 homolog; (5211:) Raf Kinase (RKI); (5212:) ralA binding protein 1 [Homo sapiens]; (5213:) RALBP1 associated Eps domain containing 2 [Homo sapiens]; (5214:) Ran binding protein 11 [Homo sapiens]; (5215:) RAN binding protein 2 [Homo sapiens]; (5216:) RAN binding protein 9 [Homo sapiens]; (5217:) Ran GTPase activating protein 1 [Homo sapiens]; (5218:) Ran GTPase-activating protein 1; (5219:) Ran-binding protein 2 (RanBP2) (Nuclear pore complex proteinNup358) (Nucleoporin Nup358) (358 kDa nucleoporin) (P270); (5220:) Ran-binding protein 9 (RanBP9) (RanBP7) (Ran-binding protein M)(RanBPM) (BPM90) (BPM-L); (5221:) RanBP-type and C3HC4-type zinc finger containing 1 isoform 1 [Homosapiens]; (5222:) RanBP-type and C3HC4-type zinc finger containing 1 isoform 2 [Homosapiens]; (5223:) RanBP-type and C3HC4-type

zinc finger-containing protein 1(Ubiquitin-conjugating enzyme 7-interacting protein 3) (Hepatitis Bvirus X-associated protein 4) (HBV-associated factor 4) (RINGfinger protein 54); (5224:) Ras-GTPase-activating protein SH3-domain-binding protein [Homosapiens]; (5225:) Ras-related C3 botulinum toxin substrate 1 precursor (p21-Rac1)(Ras-like protein TC25); (5226:) Ras-related C3 botulinum toxin substrate 2 precursor (p21-Rac2)(Small G protein) (GX); (5227:) Ras-related protein Rab-5A; (5228:) Ras-related protein Rab-5B; (5229:) Ras-related protein Rap-1A precursor (GTP-binding protein smg-p21A)(Ras-related protein Krev-1) (C21KG) (G-22K); (5230:) Ras-related protein Rap-1b precursor (GTP-binding protein smgp21B); (5231:) Ras-related protein Rap-2a (RbBP-30); (5232:) rcUBE2S [Homo sapiens]; (5233:) Receptor activity-modifying protein 1 precursor (CRLRactivity-modifying protein 1) (Calcitonin-receptor-like receptoractivity-modifying protein 1); (5234:) Receptor activity-modifying protein 2 precursor (CRLRactivity-modifying protein 2) (Calcitonin-receptor-like receptoractivity-modifying protein 2); (5235:) Receptor activity-modifying protein 3 precursor (CRLRactivity-modifying protein 3) (Calcitonin-receptor-like receptoractivity-modifying protein 3); (5236:) Receptor Gamma (RXR Gamma); (5237:) Receptor tyrosine-protein kinase erbB-2 precursor (p185erbB2)(C-erbB-2) (NEU proto-oncogene) (Tyrosine kinase-type cell surfacereceptor HER2) (MLN 19) (CD340 antigen); (5238:) Receptor tyrosine-protein kinase erbB-3 precursor (c-erbB3)(Tyrosine kinase-type cell surface receptor HER3); (5239:) Receptor tyrosine-protein kinase erbB-4 precursor (p180erbB4)(Tyrosine kinase-type cell surface receptor HER4); (5240:) Receptor-binding cancer antigen expressed on SiSo cells(Cancer-associated surface antigen RCAS1) (Estrogenreceptor-binding fragment-associated gene 9 protein); (5241:) receptor-interacting serine-threonine kinase 2 [Homo sapiens]; (5242:) Receptor-type tyrosine-protein phosphatase delta precursor(Protein-tyrosine phosphatase delta) (R-PTP-delta); (5243:) Receptor-type tyrosine-protein phosphatase F precursor (LARprotein) (Leukocyte antigen related); (5244:) Receptor-type tyrosine-protein phosphatase kappa precursor(Protein-tyrosine phosphatase kappa) (R-PTP-kappa); (5245:) Receptor-type tyrosine-protein phosphatase mu precursor(Protein-tyrosine phosphatase mu) (R-PTP-mu); (5246:) Receptor-type tyrosine-protein phosphatase N2 precursor (R-PTP-N2)(Islet cell autoantigen-related protein) (ICAAR) (IAR) (Phogrin); (5247:) Receptor-type tyrosine-protein phosphatase O precursor (Glomerularepithelial protein 1) (Protein tyrosine phosphatase U2) (PTPase U2)(PTP-U2); (5248:) Receptor-type tyrosine-protein phosphatase R precursor(Protein-tyrosine phosphatase PCPTP1) (NC-PTPCOM1) (Ch-1PTPase);

(5249:) Receptor-type tyrosine-protein phosphatase S precursor (R-PTP-S)(Protein-tyrosine phosphatase sigma) (R-PTP-sigma); (5250:) Receptor-type tyrosine-protein phosphatase T precursor (R-PTP-T)(RPTP-rho); (5251:) Receptor-type tyrosine-protein phosphatase U precursor (R-PTP-U)(Protein-tyrosine phosphatase J) (PTP-J) (Pancreatic carcinomaphosphatase 2) (PCP-2); (5252:) Receptor-type tyrosine-protein phosphatase-like N precursor(R-PTP-N) (PTP IA-2) (Islet cell antigen 512) (ICA 512) (Islet cellautoantigen 3); (5253:) RECK protein precursor [Homo sapiens]; (5254:) RecQ protein-like isoform 1 [Homo sapiens]; (5255:) redox active peptide; (5256:) Red-sensitive opsin (Red cone photoreceptor pigment); (5257:) reductase,dihydrofolate; (5258:) Ref-1 [Homo sapiens]; (5259:) regenerating islet-derived 1 alpha precursor [Homo sapiens]; (5260:) Relaxin receptor 1 (Relaxin family peptide receptor 1)(Leucine-rich repeat-containing G-protein coupled receptor 7); (5261:) Relaxin receptor 2 (Relaxin family peptide receptor 2)(Leucine-rich repeat-containing G-protein coupled receptor 8)(G-protein coupled receptor affecting testicular descent)(G-protein coupled receptor 106); (5262:) Relaxin-3 receptor 1 (RLN3 receptor 1) (Relaxin family peptidereceptor 3) (Somatostatin- and angiotensin-like peptide receptor)(G protein-coupled receptor SALPR) (GPCR135); (5263:) Relaxin-3 receptor 2 (Relaxin family peptide receptor 4) (G-proteincoupled receptor 100) (GPCR142); (5264:) Renin; (5265:) renin binding protein [Homo sapiens]; (5266:) Renin precursor (Angiotensinogenase); (5267:) Renin receptor precursor (Renin/prorenin receptor) (ATPaseH(+)-transporting lysosomal accessory protein 2) (ATPaseH(+)-transporting lysosomal-interacting protein 2) (Vacuolar ATPsynthase membrane sector-associated protein M8-9) (V-ATPase M8.9subunit) (ATP6M8-9) (N14F) (ER-localized type I transmembraneadaptor) (Embryonic liver differentiation factor 10); (5268:) resistin [Homo sapiens]; (5269:) Ret Receptor Tyrosine Kinase Stimulator; (5270:) Reticulon-4 receptor precursor (Nogo receptor) (NgR) (Nogo-66receptor); (5271:) Reticulon-4 receptor-like 1 precursor (Nogo-66 receptor homolog 2)(Nogo-66 receptor-related protein 3) (NgR3) (Nogo receptor-like 2); (5272:) Reticulon-4 receptor-like 2 precursor (Nogo-66 receptor homolog 1)(Nogo-66 receptor-related protein 2) (NgR2) (Nogo receptor-like 3); (5273:) retina copper-containing monoamine oxidase [Homo sapiens]; (5274:) Retinal dehydrogenase 1 (RalDH1) (RALDH 1) (Aldehyde dehydrogenasefamily 1 member A1) (Aldehyde dehydrogenase, cytosolic) (ALHDII)(ALDH-E1); (5275:) Retinal guanylyl cyclase 1 precursor (Guanylate cyclase 2D,retinal) (RETGC-1) (Rod outer segment membrane guanylate cyclase)(ROS-GC); (5276:) Retinal guanylyl cyclase 2 precursor (Guanylate cyclase 2F,retinal) (RETGC-2) (Rod outer segment

membrane guanylate cyclase 2)(ROS-GC2) (Guanylate cyclase F) (GC-F); (5277:) retinal pigment epithelium-specific protein 65kDa [Homo sapiens]; (5278:) retina-specific amine oxidase [Homo sapiens]; (5279:) Retina-specific copper amine oxidase precursor (RAO) (Amine oxidase[copper-containing]); (5280:) retinoblastoma 1 [Homo sapiens]; (5281:) retinoblastoma-like 2 (p130) [Homo sapiens]; (5282:) retinoic acid hydroxylase [Homo sapiens]; (5283:) Retinoic acid receptor alpha (RAR-alpha); (5284:) Retinoic acid receptor beta (RAR-beta) (RAR-epsilon) (HBV-activatedprotein); (5285:) Retinoic acid receptor gamma-1 (RAR-gamma-1); (5286:) Retinoic acid receptor gamma-2 (RAR-gamma-2); (5287:) Retinoic acid receptor RXR-alpha (Retinoid X receptor alpha); (5288:) Retinoic acid receptor RXR-beta (Retinoid X receptor beta); (5289:) Retinoic acid receptor RXR-gamma (Retinoid X receptor gamma); (5290:) Retinoic Acid Receptor-Alpha (RAR Alpha); (5291:) Retinoic Acid Receptor-Beta (RAR Beta); (5292:) Retinoic Acid Receptor-Gamma (RAR Gamma); (5293:) Retinoic acid-induced protein 3 (G-protein coupled receptor familyC group 5 member A) (Retinoic acid-induced gene 1 protein) (RAIG-1)(Orphan G-protein coupling receptor PEIG-1); (5294:) Retinoic X Receptor Alpha (RXR Alpha); (5295:) Retinoic X Receptor Beta (RXR Beta); (5296:) retinoid X receptor, alpha [Homo sapiens]; (5297:) Retinol Dehydrogenase; (5298:) Retinol dehydrogenase 12 (All-trans and 9-cis retinoldehydrogenase); (5299:) retinol dehydrogenase 12 (all-trans and 9-cis) [Homo sapiens]; (5300:) Retinol dehydrogenase 13; (5301:) retinol dehydrogenase 16 [Homo sapiens]; (5302:) retinol dehydrogenase 5 (11-cis and 9-cis) [Homo sapiens]; (5303:) retinol dehydrogenase 8 (all-trans) [Homo sapiens]; (5304:) rhabdomyosarcoma antigen MU-RMS-40.10E [Homo sapiens]; (5305:) Rho GTPase Protein; (5306:) Rho-associated protein kinase 1 (Rho-associated,coiled-coil-containing protein kinase 1) (p160 ROCK-1) (p160ROCK)(NY-REN-35 antigen); (5307:) Rho-associated protein kinase 2 (Rho-associated,coiled-coil-containing protein kinase 2) (p164 ROCK-2) (Rho kinase2); (5308:) Rho-associated, coiled-coil containing protein kinase 1 [Homosapiens]; (5309:) Rhodopsin (Opsin-2); (5310:) Rho-Kinase; (5311:) Rho-related GTP-binding protein RhoQ (Ras-related GTP-bindingprotein TC10); (5312:) Ribonuclease 4 precursor (RNase 4); (5313:) Ribonuclease H1 (RNase H1) (Ribonuclease H type II); (5314:) ribonuclease H1 [Homo sapiens]; (5315:) Ribonuclease H2 subunit A (RNase H2 subunit A) (Ribonuclease HIsubunit A) (Ribonuclease HI large subunit) (RNase HI large subunit)(RNase H(35)) (Aicardi-Goutieres syndrome 4 protein) (AGS4); (5316:) ribonuclease HI, large subunit [Homo sapiens]; (5317:) ribonuclease III, nuclear [Homo sapiens]; (5318:)

ribonuclease, RNase A family, 4 precursor [Homo sapiens]; (5319:) Ribonucleoside-diphosphate reductase large subunit(Ribonucleoside-diphosphate reductase M1 subunit) (Ribonucleotidereductase large chain); (5320:) ribonucleoside-diphosphate reductase M1 chain [Homo sapiens]; (5321:) Ribonucleotide Reductase (RR); (5322:) Ribose-phosphate pyrophosphokinase I (Phosphoribosyl pyrophosphatesynthetase I) (PRS-I) (PPRibP); (5323:) Ribose-phosphate pyrophosphokinase II (Phosphoribosyl pyrophosphatesynthetase II) (PRS-II) (PPRibP); (5324:) Ribose-phosphate pyrophosphokinase III (Phosphoribosylpyrophosphate synthetase III) (PRS-III) (Phosphoribosylpyrophosphate synthetase 1-like 1); (5325:) Ribosomal protein S6 kinase alpha-1 (S6K-alpha 1) (90 kDa ribosomalprotein S6 kinase 1) (p90-RSK 1) (Ribosomal S6 kinase 1) (RSK-1)(pp90RSK1) (p90S6K) (MAP kinase-activated protein kinase 1a)(MAPKAPK1A); (5326:) Ribosomal protein S6 kinase alpha-2 (S6K-alpha 2) (90 kDa ribosomalprotein S6 kinase 2) (p90-RSK 2) (Ribosomal S6 kinase 3) (RSK-3)(pp90RSK3) (MAP kinase-activated protein kinase 1c) (MAPKAPK1C); (5327:) Ribosomal protein S6 kinase alpha-3 (S6K-alpha 3) (90 kDa ribosomalprotein S6 kinase 3) (p90-RSK 3) (Ribosomal S6 kinase 2) (RSK-2)(pp90RSK2) (Insulin-stimulated protein kinase 1) (ISPK-1) (MAPkinase-activated protein kinase 1b) (MAPKAPK1B); (5328:) Ribosomal protein S6 kinase alpha-4 (Nuclear mitogen-andstress-activated protein kinase 2) (90 kDa ribosomal protein S6kinase 4) (Ribosomal protein kinase B) (RSKB); (5329:) Ribosomal protein S6 kinase alpha-5 (Nuclear mitogen-andstress-activated protein kinase 1) (90 kDa ribosomal protein S6kinase 5) (RSK-like protein kinase) (RSKL); (5330:) Ribosomal protein S6 kinase alpha-6 (S6K-alpha 6) (90 kDa ribosomalprotein S6 kinase 6) (p90-RSK 6) (Ribosomal S6 kinase 4) (RSK-4)(pp90RSK4); (5331:) Ribosomal protein S6 kinase beta-1 (Ribosomal protein S6 kinase I)(S6K) (S6K1) (70 kDa ribosomal protein S6 kinase 1) (p70 S6 kinasealpha) (p70(S6K)-alpha) (p70-S6K) (P70S6K) (p70-alpha); (5332:) Ribosyldihydronicotinamide dehydrogenase [quinone] (NRHdehydrogenase [quinone] 2) (Quinone reductase 2) (QR2) (NRH:quinoneoxidoreductase 2); (5333:) RING finger and WD repeat domain protein 2 (Ubiquitin-proteinligase COP1) (Constitutive photomorphogenesis protein 1 homolog)(hCOP1); (5334:) RING finger protein 125 (T-cell RING activation protein 1)(TRAC-1); (5335:) RING finger protein 139 (Translocation in renal carcinoma onchromosome 8); (5336:) ring finger protein 139 [Homo sapiens]; (5337:) ring finger protein 144 [Homo sapiens]; (5338:) ring finger protein 2 [Homo sapiens]; (5339:) ring finger protein 25 [Homo sapiens]; (5340:) RING finger protein 25;

(5341:) RING finger protein 37 (Ubiquitin-conjugating enzyme 7-interactingprotein 5) (U-box domain-containing protein 5); (5342:) ring finger protein 41 isoform 1 [Homo sapiens]; (5343:) ring finger protein 41 isoform 2 [Homo sapiens]; (5344:) ring finger protein 7 isoform 1 [Homo sapiens]; (5345:) ring finger protein 7 isoform 3 [Homo sapiens]; (5346:) RING-box protein 1 (Rbx1) (Regulator of cullins 1) (RING fingerprotein 75) (Protein ZYP); (5347:) RING-box protein 2 (Rbx2) (RING finger protein 7) (Regulator ofcullins 2) (CKII beta-binding protein 1) (CKBBP1) (Sensitive toapoptosis gene protein); (5348:) RNA (guanine-7-) methyltransferase [Homo sapiens]; (5349:) RNA (guanine-N7-) methyltransferase [Homo sapiens]; (5350:) RNA 3'-terminal phosphate cyclase (RNA-3'-phosphate cyclase) (RNAcyclase); (5351:) RNA cyclase homolog [Homo sapiens]; (5352:) RNA guanylyltransferase and 5'-phosphatase [Homo sapiens]; (5353:) RNA lariat debranching enzyme [Homo sapiens]; (5354:) RNA polymerase I-associated factor PAF49 (Anti-sense to ERCC-1protein) (ASE-1) (CD3-epsilon-associated protein) (CD3E-associatedprotein) (CAST); (5355:) RNA polymerase II transcription factor SIII p18 subunit; (5356:) RNA polymerase III subunit RPC155-A [Homo sapiens]; (5357:) RNA polymerase III subunit RPC155-B [Homo sapiens]; (5358:) RNA polymerase III subunit RPC155-C [Homo sapiens]; (5359:) RNA polymerase III subunit RPC155-D [Homo sapiens]; (5360:) RNA polymerase III subunit RPC62 [Homo sapiens]; (5361:) RNA polymerase transcriptional regulation mediator, subunit 6homolog (Activator-recruited cofactor 33 kDa component) (ARC33)(NY-REN-28 antigen); (5362:) RNA-specific adenosine deaminase B1 isoform 1 [Homo sapiens]; (5363:) RNA-specific adenosine deaminase B1 isoform 2 [Homo sapiens]; (5364:) RNA-specific adenosine deaminase B1 isoform 3 [Homo sapiens]; (5365:) RNA-specific adenosine deaminase B1 isoform 4 [Homo sapiens]; (5366:) RNPEPL1 protein [Homo sapiens]; (5367:) Roundabout homolog 1 precursor (H-Robo-1) (Deleted in U twentytwenty); (5368:) Roundabout homolog 3 precursor (Roundabout-like protein 3); (5369:) Roundabout homolog 4 precursor (Magic roundabout); (5370:) RP11-235O14.2 [Homo sapiens]; (5371:) RPE-retinal G protein-coupled receptor; (5372:) "R-type pyruvate kinase; R-type PK [Homo sapiens]."; (5373:) Ryanodine Receptor 1 (RYR1); (5374:) Ryanodine receptor 1 (Skeletal muscle-type ryanodine receptor)(RyR1) (RYR-1) (Skeletal muscle calcium release channel); (5375:) Ryanodine receptor 2 (Cardiac muscle-type ryanodine receptor)(RyR2) (RYR-2) (Cardiac muscle ryanodine receptor-calcium releasechannel) (hRYR-2); (5376:) Ryanodine receptor 3 (Brain-type ryanodine receptor) (RyR3) (RYR-3)(Brain ryanodine receptor-calcium release channel); (5377:) S100 calcium-binding protein

A8 [Homo sapiens]; (5378:) S100 calcium-binding protein A9 [Homo sapiens]; (5379:) SA [Homo sapiens]; (5380:) SA hypertension-associated homolog isoform 2 [Homo sapiens]; (5381:) S-adenosylhomocysteine hydrolase [Homo sapiens]; (5382:) S-adenosylmethionine decarboxylase (SAMDC); (5383:) S-adenosylmethionine decarboxylase 1 isoform 1 precursor [Homosapiens]; (5384:) S-adenosylmethionine decarboxylase 1 isoform 2 [Homo sapiens]; (5385:) "S-adenosylmethionine decarboxylase proenzyme (AdoMetDC) (SamDC)[Contains:) S-adenosylmethionine decarboxylase alpha chain;S-adenosylmethionine decarboxylase beta chain]."; (5386:) Salivary alpha-amylase precursor (1,4-alpha-D-glucanglucanohydrolase); (5387:) sarco/endoplasmic reticulum Ca2+ -ATPase isoform a [Homo sapiens]; (5388:) sarco/endoplasmic reticulum Ca2+ -ATPase isoform b [Homo sapiens]; (5389:) sarco/endoplasmic reticulum Ca2+ -ATPase isoform c [Homo sapiens]; (5390:) sarco/endoplasmic reticulum Ca2+ -ATPase isoform d [Homo sapiens]; (5391:) sarco/endoplasmic reticulum Ca2+ -ATPase isoform e [Homo sapiens]; (5392:) sarco/endoplasmic reticulum Ca2+ -ATPase isoform f [Homo sapiens]; (5393:) Sarcoplasmic/endoplasmic reticulum calcium ATPase 1 (Calcium pump1) (SERCA1) (SR Ca(2+)-ATPase 1) (Calcium-transporting ATPasesarcoplasmic reticulum type, fast twitch skeletal muscle isoform)(Endoplasmic reticulum class 1/2 Ca(2+) ATPase); (5394:) Sarcoplasmic/endoplasmic reticulum calcium ATPase 2 (Calcium pump2) (SERCA2) (SR Ca(2+)-ATPase 2) (Calcium-transporting ATPasesarcoplasmic reticulum type, slow twitch skeletal muscle isoform)(Endoplasmic reticulum class 1/2 Ca(2+) ATPase); (5395:) Sarcoplasmic/endoplasmic reticulum calcium ATPase 3 (Calcium pump3) (SERCA3) (SR Ca(2+)-ATPase 3); (5396:) SARS Virus Protease; (5397:) scavenger mRNA decapping enzyme [Homo sapiens]; (5398:) Scavenger mRNA decapping enzyme DcpS (DCS-1) (Hint-related7meGMP-directed hydrolase) (Histidine triad protein member 5)(HINT-5); (5399:) Scavenger receptor class B member 1 (SRB1) (SR-BI) (CD36antigen-like 1) (CD36 and LIMPII analogous 1) (CLA-1) (Collagentype I receptor, thrombospondin receptor-like 1); (5400:) scavenger receptor class B, member 1 [Homo sapiens]; (5401:) Scavenger receptor class F member 2 precursor (Scavenger receptorexpressed by endothelial cells 2 protein) (SREC-II) (SRECRP-1); (5402:) SDS protein [Homo sapiens]; (5403:) SDSL protein [Homo sapiens]; (5404:) SEC14-like 2 [Homo sapiens]; (5405:) SECIS binding protein 2 [Homo sapiens]; (5406:) Secreted Apoptosis-Related Protein 2 (SARP2); (5407:) Secretin Receptor (SCTR); (5408:) Secretin receptor precursor (SCT-R); (5409:) Secretory Leukocyte Protease (SLPI); (5410:) Secretory

Phospholipase A2 (sPLA2); (5411:) Secretory Protein Clusterin (sCLU); (5412:) selectin E precursor [Homo sapiens]; (5413:) selectin L precursor [Homo sapiens]; (5414:) selectin P ligand [Homo sapiens]; (5415:) selectin P precursor [Homo sapiens]; (5416:) selenocysteine lyase [Homo sapiens]; (5417:) selenophosphate synthetase [Homo sapiens]; (5418:) selenophosphate synthetase 2 [Homo sapiens]; (5419:) Semaphorin-4D precursor (Leukocyte activation antigen CD100) (BB18)(A8) (GR3); (5420:) Semicarbazide-Sensitive Amine Oxidase (SSAO); (5421:) Sentrin-specific protease 8 (Sentrin/SUMO-specific protease SENP8)(Protease, cysteine 2) (NEDD8-specific protease 1) (Deneddylase-1); (5422:) Separin (Separase) (Caspase-like protein ESPL1) (Extra spindlepoles-like 1 protein); (5423:) sepiapterin reductase (7,8-dihydrobiopterin:NADP+ oxidoreductase)[Homo sapiens]; (5424:) Sepiapterin reductase (SPR); (5425:) sepiapterin reductase; (5426:) Serase-1B [Homo sapiens]; (5427:) serine (or cysteine) proteinase inhibitor, clade A (alpha-1antiproteinase, antitrypsin), member 1 [Homo sapiens]; (5428:) serine (or cysteine) proteinase inhibitor, clade B (ovalbumin),member 2 [Homo sapiens]; (5429:) serine (or cysteine) proteinase inhibitor, clade B (ovalbumin),member 9 [Homo sapiens]; (5430:) serine (or cysteine) proteinase inhibitor, clade I (neuroserpin),member 1 [Homo sapiens]; (5431:) serine dehydratase (EC 4.2.1.13); (5432:) serine dehydratase [Homo sapiens]; (5433:) serine dehydratase-2 [Homo sapiens]; (5434:) serine dehydratase-like [Homo sapiens]; (5435:) serine hydroxymethyltransferase 1 (soluble) isoform 1 [Homosapiens]; (5436:) serine hydroxymethyltransferase 1 (soluble) isoform 2 [Homosapiens]; (5437:) Serine hydroxymethyltransferase, cytosolic (Serine methylase)(Glycine hydroxymethyltransferase) (SHMT); (5438:) Serine hydroxymethyltransferase, mitochondrial precursor (Serinemethylase) (Glycine hydroxymethyltransferase) (SHMT); (5439:) serine palmitoyltransferase (SPT); (5440:) Serine palmitoyltransferase 1 (Long chain base biosynthesis protein1) (LCB 1) (Serine-palmitoyl-CoA transferase 1) (SPT 1) (SPT1); (5441:) Serine palmitoyltransferase 2 (Long chain base biosynthesis protein2) (LCB 2) (Serine-palmitoyl-CoA transferase 2) (SPT 2); (5442:) serine palmitoyltransferase subunit 1 isoform a [Homo sapiens]; (5443:) serine palmitoyltransferase subunit 1 isoform b [Homo sapiens]; (5444:) serine palmitoyltransferase, long chain base subunit 2 [Homosapiens]; (5445:) serine palmitoyltransferase, subunit I [Homo sapiens]; (5446:) serine palmitoyltransferase, subunit II [Homo sapiens]; (5447:) serine protease inhibitor, Kazal type 1 [Homo sapiens]; (5448:) serine racemase [Homo sapiens]; (5449:) Serine racemase; (5450:) serine/threonine kinase 16 [Homo sapiens]; (5451:) Serine/threonine kinase NLK (Nemo-like kinase) (Protein

LAK1); (5452:) Serine/threonine-protein kinase 25 (Sterile 20/oxidantstress-response kinase 1) (Ste20/oxidant stress response kinase 1)(SOK-1) (Ste20-like kinase); (5453:) Serine/threonine-protein kinase 3 (STE20-like kinase MST2) (MST-2)(Mammalian STE20-like protein kinase 2) (Serine/threonine-proteinkinase Krs-1); (5454:) Serine/threonine-protein kinase 36 (Fused homolog); (5455:) Serine/threonine-protein kinase 38 (NDR1 protein kinase) (NuclearDbf2-related kinase 1); (5456:) Serine/threonine-protein kinase 38-like (NDR2 protein kinase)(Nuclear Dbf2-related kinase 2); (5457:) Serine/threonine-protein kinase 4 (STE20-like kinase MST1) (MST-1)(Mammalian STE20-like protein kinase 1) (Serine/threonine-proteinkinase Krs-2); (5458:) Serine/threonine-protein kinase ATR (Ataxia telangiectasia andRad3-related protein) (FRAP-related protein 1); (5459:) Serine/threonine-protein kinase Chk2 (Cds1); (5460:) Serine/threonine-protein kinase D1 (nPKC-D1) (Protein kinase D)(Protein kinase C mu type) (nPKC-mu); (5461:) Serine/threonine-protein kinase D2 (nPKC-D2); (5462:) Serine/threonine-protein kinase D3 (Protein kinase C nu type)(nPKC-nu) (Protein kinase EPK2); (5463:) Serine/threonine-protein kinase H1 (PSK-H1); (5464:) Serine/threonine-protein kinase ICK (Intestinal cell kinase) (hICK)(MAK-related kinase) (MRK) (Laryngeal cancer kinase 2) (LCK2); (5465:) Serine/threonine-protein kinase MARK1 (MAP/microtubuleaffinity-regulating kinase 1); (5466:) Serine/threonine-protein kinase MARK2 (MAP/microtubuleaffinity-regulating kinase 2) (ELKL motif kinase) (EMK1) (PAR1homolog); (5467:) Serine/threonine-protein kinase MRCK alpha (CDC42-binding proteinkinase alpha) (Myotonic dystrophy kinase-related CDC42-bindingkinase alpha) (Myotonic dystrophy protein kinase-like alpha) (MRCKalpha) (DMPK-like alpha); (5468:) Serine/threonine-protein kinase MRCK beta (CDC42-binding proteinkinase beta) (Myotonic dystrophy kinase-related CDC42-bindingkinase beta) (Myotonic dystrophy protein kinase-like beta) (MRCKbeta) (DMPK-like beta); (5469:) Serine/threonine-protein kinase MRCK gamma (CDC42-binding proteinkinase gamma) (Myotonic dystrophy kinase-related CDC42-bindingkinase gamma) (Myotonic dystrophy protein kinase-like alpha) (MRCKgamma) (DMPK-like gamma); (5470:) Serine/threonine-protein kinase MST4 (STE20-like kinase MST4)(MST-4) (Mammalian STE20-like protein kinase 4)(Serine/threonine-protein kinase MASK) (Mst3 and SOK1-relatedkinase); (5471:) Serine/threonine-protein kinase N1 (Protein kinase C-like 1)(Protein-kinase C-related kinase 1) (Protein kinase C-like PKN)(Serine-threonine protein kinase N) (Protein kinase PKN-alpha); (5472:) Serine/threonine-protein kinase N2 (Protein kinase C-like 2)(Protein-kinase C-related kinase 2); (5473:) Serine/threonine-protein

kinase Nek11 (NimA-related protein kinase11) (Never in mitosis A-related kinase 11); (5474:) Serine/threonine-protein kinase Nek2 (NimA-related protein kinase2) (NimA-like protein kinase 1) (HSPK 21); (5475:) Serine/threonine-protein kinase Nek9 (NimA-related protein kinase9) (Never in mitosis A-related kinase 9) (Nercc1 kinase)(NIMA-related kinase 8) (Nek8); (5476:) Serine/threonine-protein kinase NIM1; (5477:) Serine/threonine-protein kinase OSR1 (Oxidative stress-responsive 1protein); (5478:) Serine/threonine-protein kinase PAK 1 (p21-activated kinase 1)(PAK-1) (P65-PAK) (Alpha-PAK); (5479:) Serine/threonine-protein kinase PAK 2 (p21-activated kinase 2)(PAK-2) (PAK65) (Gamma-PAK) (S6/H4 kinase); (5480:) Serine/threonine-protein kinase PAK 3 (p21-activated kinase 3)(PAK-3) (Beta-PAK) (Oligophrenin-3); (5481:) Serine/threonine-protein kinase receptor R3 precursor (SKR3)(Activin receptor-like kinase 1) (ALK-1) (TGF-B superfamilyreceptor type I) (TSR-I); (5482:) Serine/threonine-protein kinase SMG1 (SMG-1) (hSMG-1) (Lambda/iotaprotein kinase C-interacting protein) (Lambda-interacting protein)(61E3.4); (5483:) Serine/threonine-protein kinase SNF1-like kinase 1(Serine/threonine-protein kinase SNF1LK); (5484:) Serine/threonine-protein kinase SNF1-like kinase 2 (Qin-inducedkinase); (5485:) Serine/threonine-protein kinase SRPK1 (Serine/arginine-richprotein-specific kinase 1) (SR-protein-specific kinase 1) (SFRSprotein kinase 1); (5486:) Serine/threonine-protein kinase SRPK2 (Serine/arginine-richprotein-specific kinase 2) (SR-protein-specific kinase 2) (SFRSprotein kinase 2); (5487:) Serine/threonine-protein kinase TBK1 (TANK-binding kinase 1) (T2K)(NF-kappa-B-activating kinase); (5488:) Serine/threonine-protein kinase tousled-like 1 (Tousled-like kinase1) (PKU-beta); (5489:) Serine/threonine-protein kinase tousled-like 2 (Tousled-like kinase2) (PKU-alpha); (5490:) Serine/threonine-protein kinase VRK1 (Vaccinia-related kinase 1); (5491:) Serine/threonine-protein kinase WNK1 (Protein kinase with no lysine1) (Protein kinase, lysine-deficient 1) (Kinase deficient protein); (5492:) Serine/threonine-protein kinase WNK2 (Protein kinase with no lysine2) (Protein kinase, lysine-deficient 2); (5493:) Serine/threonine-protein kinase WNK3 (Protein kinase with no lysine3) (Protein kinase, lysine-deficient 3); (5494:) Serine/threonine-protein kinase WNK4 (Protein kinase with no lysine4) (Protein kinase, lysine-deficient 4); (5495:) "Serine/threonine-protein kinase/endoribonuclease IRE1 precursor(Inositol-requiring protein 1) (hIRE1p) (IRE1a) (Ire1-alpha)(Endoplasmic reticulum-to-nucleus signaling 1) [Includes:Serine/threonine-protein kinase ; Endoribonuclease]."; (5496:) "Serine/threonine-protein kinase/endoribonuclease IRE2 precursor(Inositol-requiring protein 2) (hIRE2p) (IRE1b) (Ire1-beta)(Endoplasmic reticulum-to-nucleus signaling

2) [Includes:Serine/threonine-protein kinase ; Endoribonuclease]."; (5497:) Serine/threonine-protein phosphatase 2A 48 kDa regulatory subunit B(PP2A, subunit B, PR48 isoform); (5498:) Serine/threonine-protein phosphatase 2A 55 kDa regulatory subunit Balpha isoform (PP2A, subunit B, B-alpha isoform) (PP2A, subunit B,B55-alpha isoform) (PP2A, subunit B, PR55-alpha isoform) (PP2A,subunit B, R2-alpha isoform); (5499:) Serine/threonine-protein phosphatase 2A 55 kDa regulatory subunit Bbeta isoform (PP2A, subunit B, B-beta isoform) (PP2A, subunit B,B55-beta isoform) (PP2A, subunit B, PR55-beta isoform) (PP2A,subunit B, R2-beta isoform); (5500:) Serine/threonine-protein phosphatase 2A 55 kDa regulatory subunit Bdelta isoform (PP2A, subunit B, B-delta isoform) (PP2A, subunit B,B55-delta isoform) (PP2A, subunit B, PR55-delta isoform) (PP2A,subunit B, R2-delta isoform); (5501:) Serine/threonine-protein phosphatase 2A 55 kDa regulatory subunit Bgamma isoform (PP2A, subunit B, B-gamma isoform) (PP2A, subunit B,B55-gamma isoform) (PP2A, subunit B, PR55-gamma isoform) (PP2A,subunit B, R2-gamma isoform) (IMYPNO1); (5502:) Serine/threonine-protein phosphatase 2A 56 kDa regulatory subunitalpha isoform (PP2A, B subunit, B' alpha isoform) (PP2A, B subunit,B56 alpha isoform) (PP2A, B subunit, PR61 alpha isoform) (PP2A, Bsubunit, R5 alpha isoform); (5503:) Serine/threonine-protein phosphatase 2A 56 kDa regulatory subunitbeta isoform (PP2A, B subunit, B' beta isoform) (PP2A, B subunit,B56 beta isoform) (PP2A, B subunit, PR61 beta isoform) (PP2A, Bsubunit, R5 beta isoform); (5504:) Serine/threonine-protein phosphatase 2A 56 kDa regulatory subunitdelta isoform (PP2A, B subunit, B' delta isoform) (PP2A, B subunit,B56 delta isoform) (PP2A, B subunit, PR61 delta isoform) (PP2A, Bsubunit, R5 delta isoform); (5505:) Serine/threonine-protein phosphatase 2A 56 kDa regulatory subunitepsilon isoform (PP2A, B subunit, B' epsilon isoform) (PP2A, Bsubunit, B56 epsilon isoform) (PP2A, B subunit, PR61 epsilonisoform) (PP2A, B subunit, R5 epsilon isoform); (5506:) Serine/threonine-protein phosphatase 2A 56 kDa regulatory subunitgamma isoform (PP2A, B subunit, B' gamma isoform) (PP2A, B subunit,B56 gamma isoform) (PP2A, B subunit, PR61 gamma isoform) (PP2A, Bsubunit, R5 gamma isoform) (NY-REN-29 antigen); (5507:) Serine/threonine-protein phosphatase 2A 65 kDa regulatory subunit Abeta isoform (PP2A, subunit A, PR65-beta isoform) (PP2A, subunit A,R1-beta isoform); (5508:) Serine/threonine-protein phosphatase 2A 65 kDa regulatory subunit Aalpha isoform (PP2A, subunit A, PR65-alpha isoform) (PP2A, subunitA, R1-alpha isoform) (Medium tumor antigen-associated 61 kDaprotein); (5509:) Serine/threonine-protein phosphatase 2A 72/130 kDa regulatorysubunit B (PP2A, subunit B, B"-PR72/PR130) (PP2A, subunit

B,B72/B130 isoforms) (PP2A, subunit B, PR72/PR130 isoforms) (PP2A,subunit B, R3 isoform); (5510:) Serine/threonine-protein phosphatase 2A catalytic subunit alphaisoform (PP2A-alpha) (Replication protein C) (RP-C); (5511:) Serine/threonine-protein phosphatase 2A catalytic subunit betaisoform (PP2A-beta); (5512:) Serine/threonine-protein phosphatase 2A regulatory subunit B'(PP2A, subunit B', PR53 isoform) (Phosphotyrosyl phosphataseactivator) (PTPA); (5513:) Serine/threonine-protein phosphatase with EF-hands 1 (PPEF-1)(Protein phosphatase with EF calcium-binding domain) (PPEF)(Serine/threonine-protein phosphatase 7) (PP7); (5514:) Serine/threonine-protein phosphatase with EF-hands 2 (PPEF-2); (5515:) Serine-protein kinase ATM (Ataxia telangiectasia mutated) (A-T,mutated); (5516:) serum albumin precursor [Homo sapiens]; (5517:) Serum paraoxonase/arylesterase 1 (PON 1) (Serumaryldialkylphosphatase 1) (A-esterase 1) (Aromatic esterase 1)(K-45); (5518:) serum/glucocorticoid regulated kinase [Homo sapiens]; (5519:) seryl-tRNA synthetase [Homo sapiens]; (5520:) SET and MYND domain-containing protein 3 (Zinc finger MYNDdomain-containing protein 1); (5521:) SET domain-containing protein 7 [Homo sapiens]; (5522:) SH3-containing GRB2-like protein 2 (Endophilin-1) (Endophilin-A1)(SH3 domain protein 2A) (EEN-B1); (5523:) SH3-domain kinase-binding protein 1 (Cbl-interacting protein of 85kDa) (Human Src-family kinase-binding protein 1) (HSB-1)(CD2-binding protein 3) (CD2BP3); (5524:) short/branched chain acyl-CoA dehydrogenase [Homo sapiens]; (5525:) Short/branched chain specific acyl-CoA dehydrogenase, mitochondrialprecursor (SBCAD) (2-methyl branched chain acyl-CoA dehydrogenase)(2-MEBCAD) (2-methylbutyryl-coenzyme A dehydrogenase)(2-methylbutyryl-CoA dehydrogenase); (5526:) sialidase 2 [Homo sapiens]; (5527:) sialidase 3 [Homo sapiens]; (5528:) sialidase 4 [Homo sapiens]; (5529:) Sialidase-1 precursor (Lysosomal sialidase)(N-acetyl-alpha-neuraminidase 1) (Acetylneuraminyl hydrolase) (G9sialidase); (5530:) sialyltransferase 1 isoform a [Homo sapiens]; (5531:) sialyltransferase 1 isoform b [Homo sapiens]; (5532:) sialyltransferase 6 isoform a [Homo sapiens]; (5533:) sialyltransferase 6 isoform b [Homo sapiens]; (5534:) sialyltransferase 6 isoform c [Homo sapiens]; (5535:) sialyltransferase 6 isoform d [Homo sapiens]; (5536:) sialyltransferase 6 isoform e [Homo sapiens]; (5537:) sialyltransferase 6 isoform f [Homo sapiens]; (5538:) sialyltransferase 6 isoform g [Homo sapiens]; (5539:) sialyltransferase 6 isoform h [Homo sapiens]; (5540:) sialyltransferase 6 isoform i [Homo sapiens]; (5541:) sialyltransferase 6 isoform j [Homo sapiens]; (5542:) Sigma Receptor; (5543:) Sigma1 Receptor; (5544:) Sigma2 Receptor; (5545:) signal peptide peptidase-like 2B isoform 2 [Homo

sapiens]; (5546:) signal peptide peptidase-like 2B isoform 3 [Homo sapiens]; (5547:) Signal recognition particle receptor subunit alpha (SR-alpha)(Docking protein alpha) (DP-alpha); (5548:) Signal recognition particle receptor subunit beta (SR-beta)(Protein APMCF1); (5549:) Signal Transducer and Activator of Transcription 1 (STAT1); (5550:) Signal Transducer and Activator of Transcription 3 (STAT3); (5551:) Signal Transducer and Activator of Transcription 4 (STAT4); (5552:) Signal transducing adapter molecule 2 (STAM-2); (5553:) signal transducing adaptor molecule 1 [Homo sapiens]; (5554:) signal transducing adaptor molecule 2 [Homo sapiens]; (5555:) Signal transduction protein CBL-C (SH3-binding protein CBL-C)(CBL-3) (RING finger protein 57); (5556:) Signaling lymphocytic activation molecule precursor (IPO-3) (CD150antigen) (CDw150); (5557:) Single-strand selective monofunctional uracil DNA glycosylase; (5558:) Sirtunin 1 (SIRT1); (5559:) skeletal myosin light chain kinase [Homo sapiens]; (5560:) Skin Protease (SPI); (5561:) SLAM family member 5 precursor (Signaling lymphocytic activationmolecule 5) (Leukocyte differentiation antigen CD84) (CD84 antigen)(Cell surface antigen MAX.3) (Hly9-beta); (5562:) SLAM family member 6 precursor (NK-T-B-antigen) (NTB-A) (ActivatingNK receptor); (5563:) SLAM family member 7 precursor (CD2-like receptor activatingcytotoxic cells) (CRACC) (Protein 19A) (CD2 subset 1) (Novel Ly9)(Membrane protein FOAP-12) (CD319 antigen); (5564:) SLC27A1 protein [Homo sapiens]; (5565:) SLC27A3 protein [Homo sapiens]; (5566:) Smad ubiquitination regulatory factor 1 (Ubiquitin--protein ligaseSMURF1) (Smad-specific E3 ubiquitin ligase 1) (hSMURF1); (5567:) Smad ubiquitination regulatory factor 2 (Ubiquitin--protein ligaseSMURF2) (Smad-specific E3 ubiquitin ligase 2) (hSMURF2); (5568:) "Small inducible cytokine A14 precursor (CCL14) (ChemokineCC-1/CC-3) (HCC-1/HCC-3) (HCC-1(1-74)) (NCC-2) [Contains:HCC-1(3-74); HCC-1(4-74); HCC-1(9-74)]."; (5569:) small inducible cytokine A2 precursor [Homo sapiens]; (5570:) "Small inducible cytokine A5 precursor (CCL5) (T-cell-specificRANTES protein) (SIS-delta) (T cell-specific protein P228) (TCP228)[Contains:) RANTES(3-68); RANTES(4-68)]."; (5571:) small inducible cytokine B10 precursor [Homo sapiens]; (5572:) Small ubiquitin-related modifier 4 precursor (SUMO-4) (Smallubiquitin-like protein 4); (5573:) S-methyl-5-thioadenosine phosphorylase (5'-methylthioadenosinephosphorylase) (MTA phosphorylase) (MTAPase); (5574:) Smoothened homolog precursor (SMO) (Gx protein); (5575:) SMT3 suppressor of mif two 3 homolog 1 isoform a precursor [Homosapiens]; (5576:) SMT3 suppressor of mif two 3 homolog 1 isoform b precursor [Homosapiens]; (5577:) Sn1-specific diacylglycerol lipase alpha (DGL-

alpha) (Neural stemcell-derived dendrite regulator); (5578:) Sn1-specific diacylglycerol lipase beta (DGL-beta) (KCCR13L); (5579:) snake venom-like protease [Homo sapiens]; (5580:) SNF-related serine/threonine-protein kinase (SNF1-related kinase); (5581:) Sodium bicarbonate cotransporter 3 (Sodium bicarbonatecotransporter 2) (Sodium bicarbonate cotransporter 2b) (Bicarbonatetransporter) (Solute carrier family 4 member 7); (5582:) Sodium Hydrogen Exchange (NHE); (5583:) Sodium Hydrogen Exchange Isoform-1 (NHE-1); (5584:) Sodium Hydrogen Exchange Isoform-3 (NHE-3); (5585:) Sodium/calcium exchanger 1 precursor (Na(+)/Ca(2+)-exchange protein1); (5586:) Sodium/calcium exchanger 2 precursor (Na(+)/Ca(2+)-exchange protein2); (5587:) Sodium/calcium exchanger 3 precursor (Na(+)/Ca(2+)-exchange protein3); (5588:) Sodium/nucleoside cotransporter 2 (Na(+)/nucleoside cotransporter2) (Sodium-coupled nucleoside transporter 2) (Concentrativenucleoside transporter 2) (CNT 2) (hCNT2) (Sodium/purine nucleosideco-transporter) (SPNT); (5589:) Sodium/potassium-transporting ATPase alpha-1 chain precursor(Sodium pump 1) (Na+/K+ ATPase 1); (5590:) Sodium/potassium-transporting ATPase alpha-2 chain precursor(Sodium pump 2) (Na+/K+ ATPase 2); (5591:) Sodium/potassium-transporting ATPase alpha-3 chain (Sodium pump 3)(Na+/K+ ATPase 3) (Alpha(III)); (5592:) Sodium/potassium-transporting ATPase alpha-4 chain (Sodium pump 4)(Na+/K+ ATPase 4); (5593:) Sodium/potassium-transporting ATPase subunit beta-1(Sodium/potassium-dependent ATPase beta-1 subunit); (5594:) Sodium/potassium-transporting ATPase subunit beta-2(Sodium/potassium-dependent ATPase beta-2 subunit); (5595:) Sodium/potassium-transporting ATPase subunit beta-3(Sodium/potassium-dependent ATPase beta-3 subunit) (ATPB-3) (CD298antigen); (5596:) Sodium-Chloride Cotransporter (NCC); (5597:) Sodium-dependent phosphate transporter 1 (Solute carrier family 20member 1) (Phosphate transporter 1) (PiT-1) (Gibbon ape leukemiavirus receptor 1) (GLVR-1) (Leukemia virus receptor 1 homolog); (5598:) Sodium-Glucose Cotransporter (SGLT); (5599:) Sodium-Glucose Cotransporter Type 1 (SGLT1); (5600:) Sodium-Glucose Cotransporter Type 2 (SGLT2); (5601:) Sodium-Potassium ATPase; (5602:) Sodium-Potassium-Chloride Cotransporter; (5603:) Soluble calcium-activated nucleotidase 1 (SCAN-1) (Apyrase homolog)(Putative NF-kappa-B-activating protein 107) (PutativeMAPK-activating protein PM09); (5604:) soluble calcium-activated nucleotidase 1 [Homo sapiens]; (5605:) solute carrier family 2 (facilitated glucose transporter), member 1[Homo sapiens]; (5606:) solute carrier family 27 (fatty acid transporter), member 2 [Homosapiens]; (5607:) solute carrier family 7 (cationic

amino acid transporter, y+system), member 1 [Homo sapiens]; (5608:) solute carrier family 7, member 2 isoform 1 [Homo sapiens]; (5609:) solute carrier family 7, member 2 isoform 2 [Homo sapiens]; (5610:) Somatostatin Receptor (SSTR); (5611:) Somatostatin Receptor 1 (SSTR1); (5612:) Somatostatin Receptor 2 (SSTR2); (5613:) Somatostatin Receptor 3 (SSTR3); (5614:) Somatostatin Receptor 5 (SSTR5); (5615:) Somatostatin receptor type 1 (SS1R) (SRIF-2); (5616:) Somatostatin receptor type 2 (SS2R) (SRIF-1); (5617:) Somatostatin receptor type 3 (SS3R) (SSR-28); (5618:) Somatostatin receptor type 4 (SS4R); (5619:) Somatostatin receptor type 5 (SS5R); (5620:) Sorbitol dehydrogenase (L-iditol 2-dehydrogenase); (5621:) sorbitol dehydrogenase [Homo sapiens]; (5622:) Sortilin precursor (Neurotensin receptor 3) (NTR3) (NT3)(Glycoprotein 95) (Gp95) (100 kDa NT receptor); (5623:) sortilin-related receptor containing LDLR class A repeatspreproprotein [Homo sapiens]; (5624:) Sortilin-related receptor precursor (Sorting protein-relatedreceptor containing LDLR class A repeats) (SorLA) (SorLA-1)(Low-density lipoprotein receptor relative with 11 ligand-bindingrepeats) (LDLR relative with 11 ligand-binding repeats) (LR11); (5625:) Sorting nexin-1; (5626:) Sorting nexin-2 (Transformation-related gene 9 protein) (TRG-9); (5627:) Sp1 transcription factor [Homo sapiens]; (5628:) spectrin, alpha, erythrocytic 1 [Homo sapiens]; (5629:) spen homolog, transcriptional regulator [Homo sapiens]; (5630:) sperm adhesion molecule 1 isoform 1 [Homo sapiens]; (5631:) sperm adhesion molecule 1 isoform 2 [Homo sapiens]; (5632:) Spermidine synthase (Putrescine aminopropyltransferase) (SPDSY); (5633:) spermidine synthase [Homo sapiens]; (5634:) Spermidine/Spermine N1-Acetyltransferase (SSAT); (5635:) spermidine/spermine N1-acetyltransferase [Homo sapiens]; (5636:) Spermine oxidase (Polyamine oxidase 1) (PAO-1) (PAOh1); (5637:) spermine synthase [Homo sapiens]; (5638:) S-phase kinase-associated protein 1A isoform a [Homo sapiens]; (5639:) S-phase kinase-associated protein 1A isoform b [Homo sapiens]; (5640:) S-phase kinase-associated protein 2 isoform 1 [Homo sapiens]; (5641:) S-phase kinase-associated protein 2 isoform 2 [Homo sapiens]; (5642:) sphingomyelin phosphodiesterase (EC 3.1.4.12) - human (fragments); (5643:) sphingomyelin phosphodiesterase [Homo sapiens]; (5644:) sphingomyelin phosphodiesterase 1, acid lysosomal isoform 1precursor [Homo sapiens]; (5645:) sphingomyelin phosphodiesterase 1, acid lysosomal isoform 2precursor [Homo sapiens]; (5646:) Sphingomyelin phosphodiesterase 3 (Neutral sphingomyelinase 2)(Neutral sphingomyelinase II) (nSMase2) (nSMase-2); (5647:) Sphingomyelin phosphodiesterase precursor (Acid sphingomyelinase)(aSMase); (5648:)

Sphingosine 1-Phosphate (S1P) Receptor; (5649:) Sphingosine 1-Phosphate Receptor 1 (S1P1); (5650:) Sphingosine 1-phosphate receptor Edg-1 (Sphingosine 1-phosphatereceptor 1) (S1P1); (5651:) Sphingosine 1-phosphate receptor Edg-3 (S1P receptor Edg-3)(Endothelial differentiation G-protein coupled receptor 3)(Sphingosine 1-phosphate receptor 3) (S1P3); (5652:) Sphingosine 1-phosphate receptor Edg-5 (S1P receptor Edg-5)(Endothelial differentiation G-protein coupled receptor 5)(Sphingosine 1-phosphate receptor 2) (S1P2); (5653:) Sphingosine 1-phosphate receptor Edg-6 (S1P receptor Edg-6)(Endothelial differentiation G-protein coupled receptor 6)(Sphingosine 1-phosphate receptor 4) (S1P4); (5654:) Sphingosine 1-phosphate receptor Edg-8 (Endothelial differentiationsphingolipid G-protein-coupled receptor 8) (Sphingosine 1-phosphatereceptor 5) (S1P5); (5655:) Sphingosine 1-phosphate receptor GPR6 (G-protein coupled receptor6); (5656:) sphingosine kinase 1 isoform 1 [Homo sapiens]; (5657:) sphingosine kinase 1 isoform 2 [Homo sapiens]; (5658:) Sphingosylphosphorylcholine receptor (Ovarian cancer G-proteincoupled receptor 1) (OGR-1) (G-protein coupled receptor 68)(GPR12A); (5659:) Spleen Tyrosine Kinase (Syk); (5660:) Squalene Synthase; (5661:) Squalene synthetase (SQS) (SS) (Farnesyl-diphosphatefarnesyltransferase) (FPP:FPP farnesyltransferase); (5662:) Sqv-8-like protein [Homo sapiens]; (5663:) Src Homology-2-Containing Protein Tyrosine Phosphatase-1 (SHP-1); (5664:) Src Tyrosine Kinase (STK); (5665:) SRC/ABL Kinase; (5666:) SRP RNA 3' adenylating enzyme/pap2 [Homo sapiens]; (5667:) SRR [Homo sapiens]; (5668:) ST3 beta-galactoside alpha-2,3-sialyltransferase 5 isoform 1 [Homosapiens]; (5669:) ST3 beta-galactoside alpha-2,3-sialyltransferase 5 isoform 2 [Homosapiens]; (5670:) ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 1 [Homosapiens]; (5671:) Stabilin-1 precursor (FEEL-1 protein) (MS-1 antigen); (5672:) Stabilin-2 precursor (FEEL-2 protein) (Fasciclin EGF-likelaminin-type EGF-like and link domain-containing scavenger receptor1) (FAS1 EGF-like and X-link domain-containing adhesion molecule 2)(Hyaluronan receptor for endocytosis) [Contains:) 190 kDa formstabilin-2 (190 kDa hyaluronan receptor for endocytosis)]; (5673:) STAM binding protein [Homo sapiens]; (5674:) STAM-binding protein (Associated molecule with the SH3 domain ofSTAM); (5675:) Staphylococcus aureus Methionyl-tRNA Synthetase (MetS); (5676:) stearoyl-CoA desaturase [Homo sapiens]; (5677:) stearoyl-CoA desaturase 4 isoform a [Homo sapiens]; (5678:) stearoyl-CoA desaturase 4 isoform b [Homo sapiens]; (5679:) steroid dehydrogenase homolog [Homo sapiens]; (5680:) Steroid hormone receptor ERR1 (Estrogen-related receptor, alpha)(ERR-alpha) (Estrogen receptor-like 1); (5681:) Steroid hormone

receptor ERR2 (Estrogen-related receptor, beta)(ERR-beta) (Estrogen receptor-like 2) (ERR beta-2); (5682:) Steroid receptor RNA activator 1 (Steroid receptor RNA activatorprotein) (SRAP); (5683:) steroid sulfatase [Homo sapiens]; (5684:) Steroid X Receptor (SXR); (5685:) steroid-5-alpha-reductase 1 [Homo sapiens]; (5686:) Steroidogenic factor 1 (STF-1) (SF-1) (Adrenal 4-binding protein)(Steroid hormone receptor Ad4BP) (Fushi tarazu factor homolog 1); (5687:) sterol O-acyltransferase (acyl-Coenzyme A:) cholesterolacyltransferase) 1 [Homo sapiens]; (5688:) sterol-C5-desaturase-like [Homo sapiens]; (5689:) steryl-sulfatase precursor [Homo sapiens]; (5690:) Stomach Acid Neutralizer; (5691:) Stratum Corneum Chymotryptic Enzyme (SCCE); (5692:) stratum corneum chymotryptic enzyme [Homo sapiens]; (5693:) stratum corneum chymotryptic enzyme preproprotein [Homo sapiens]; (5694:) stratum corneum chymotryptic enzyme; (5695:) stratum corneum tryptic enzyme [Homo sapiens]; (5696:) Stress-Associated Endoplasmic Reticulum Protein 1 (SERP1); (5697:) Substance-K receptor (SKR) (Neurokinin A receptor) (NK-2 receptor)(NK-2R) (Tachykinin receptor 2); (5698:) Substance-P receptor (SPR) (NK-1 receptor) (NK-1R) (Tachykininreceptor 1); (5699:) Substrate Binding And Catalysis By Glutathione Reductase As DerivedFrom Refined Enzyme:) Substrate Crystal Structures At 2 AngstromsResolution; (5700:) subtilisin-like proprotein convertase (EC 3.4.21.-) homolog -human; (5701:) succinate dehydrogenase complex, subunit A, flavoprotein precursor[Homo sapiens]; (5702:) succinate dehydrogenase complex, subunit B, iron sulfur (Ip) [Homosapiens]; (5703:) succinate dehydrogenase complex, subunit C isoform 1 precursor[Homo sapiens]; (5704:) succinate dehydrogenase complex, subunit C isoform 2 precursor[Homo sapiens]; (5705:) succinate dehydrogenase complex, subunit C isoform 3 precursor[Homo sapiens]; (5706:) succinate dehydrogenase complex, subunit C isoform 4 precursor[Homo sapiens]; (5707:) succinate dehydrogenase complex, subunit D precursor [Homosapiens]; (5708:) succinate dehydrogenase flavoprotein subunit; (5709:) Succinate receptor 1 (G-protein coupled receptor 91) (P2Ypurinoceptor 1-like); (5710:) Succinate semialdehyde dehydrogenase, mitochondrial precursor(NAD(+)-dependent succinic semialdehyde dehydrogenase); (5711:) succinate-CoA ligase, ADP-forming, beta subunit [Homo sapiens]; (5712:) succinyl CoA:3-oxoacid CoA transferase precursor; (5713:) Succinyl-CoA ligase [ADP-forming] beta-chain, mitochondrialprecursor (Succinyl-CoA synthetase, betaA chain) (SCS-betaA)(ATP-specific succinyl-CoA synthetase subunit beta) (NY-REN-39antigen); (5714:) Succinyl-CoA:3-ketoacid-coenzyme A transferase 1, mitochondrialprecursor (Somatic-type succinyl CoA:3-oxoacid CoA-

transferase)(Scot-S); (5715:) Succinyl-CoA:3-ketoacid-coenzyme A transferase 2, mitochondrialprecursor (Testis-specific succinyl CoA:3-oxoacid CoA-transferase)(SCOT-t); (5716:) "Sucrase-isomaltase, intestinal [Contains:) Sucrase ; Isomaltase]."; (5717:) Sulfatase; (5718:) sulfatase modifying factor 1 [Homo sapiens]; (5719:) sulfatase modifying factor 2 isoform a precursor [Homo sapiens]; (5720:) sulfatase modifying factor 2 isoform b precursor [Homo sapiens]; (5721:) sulfatase modifying factor 2 isoform c precursor [Homo sapiens]; (5722:) sulfatase modifying factor 2 isoform d precursor [Homo sapiens]; (5723:) Sulfatase-modifying factor 1 precursor(C-alpha-formyglycine-generating enzyme 1); (5724:) Sulfatase-modifying factor 2 precursor(C-alpha-formyglycine-generating enzyme 2); (5725:) sulfite oxidase [Homo sapiens]; (5726:) Sulfite oxidase, mitochondrial precursor; (5727:) Sulfonylurea Receptor 1 (SUR1); (5728:) Sulfotransferase 1A1 (Aryl sulfotransferase 1) (Phenolsulfotransferase 1) (Phenol-sulfating phenol sulfotransferase 1)(P-PST 1) (Thermostable phenol sulfotransferase) (Ts-PST)(HAST1/HAST2) (ST1A3); (5729:) sulfotransferase family, cytosolic, 1A, phenol-preferring, member 1isoform a [Homo sapiens]; (5730:) sulfotransferase family, cytosolic, 1A, phenol-preferring, member 1isoform b [Homo sapiens]; (5731:) sulfotransferase family, cytosolic, 1A, phenol-preferring, member 2[Homo sapiens]; (5732:) sulfotransferase family, cytosolic, 1A, phenol-preferring, member 3[Homo sapiens]; (5733:) sulfotransferase family, cytosolic, 1A, phenol-preferring, member 4[Homo sapiens]; (5734:) sulfotransferase family, cytosolic, 2A,dehydroepiandrosterone-preferring, member 1 [Homo sapiens]; (5735:) sulfotransferase family, cytosolic, 2B, member 1 isoform a [Homosapiens]; (5736:) sulfotransferase family, cytosolic, 2B, member 1 isoform b [Homosapiens]; (5737:) SUMO1 activating enzyme subunit 1 [Homo sapiens]; (5738:) SUMO-1 activating enzyme subunit 1 [Homo sapiens]; (5739:) SUMO1 activating enzyme subunit 2 [Homo sapiens]; (5740:) SUMO-1 activating enzyme subunit 2 [Homo sapiens]; (5741:) SUMO-1 activating enzyme subunit 2 variant [Homo sapiens]; (5742:) SUMO-1-activating enzyme E1 C subunit [Homo sapiens]; (5743:) SUMO-1-activating enzyme E1 N subunit [Homo sapiens]; (5744:) SUMO-1-conjugating enzyme UBC9 (SUMO-1-protein ligase)(Ubiquitin-conjugating enzyme E2 I) (Ubiquitin-protein ligase I)(Ubiquitin carrier protein I) (Ubiquitin carrier protein 9) (p18); (5745:) Superoxide Dismutase (SOD) Mimetic; (5746:) Superoxide dismutase [Cu-Zn]; (5747:) Superoxide Dismutase 1 (SOD1); (5748:) superoxide dismutase 1, soluble [Homo sapiens]; (5749:) suppressor of variegation 3-9 homolog 1 [Homo sapiens]; (5750:) SUR5 [Homo sapiens]; (5751:) Survivin; (5752:) SWI/SNF related,

matrix associated, actin dependent regulator ofchromatin, subfamily b, member 1 isoform a [Homo sapiens]; (5753:) SWI/SNF related, matrix associated, actin dependent regulator ofchromatin, subfamily b, member 1 isoform b [Homo sapiens]; (5754:) SWI/SNF-related matrix-associated actin-dependent regulator ofchromatin a4 [Homo sapiens]; (5755:) SWI/SNF-related matrix-associated actin-dependent regulator ofchromatin a5 [Homo sapiens]; (5756:) synapsin I [Homo sapiens]; (5757:) synapsin I isoform Ia [Homo sapiens]; (5758:) synapsin I isoform Ib [Homo sapiens]; (5759:) Synapsin-1 (Synapsin I) (Brain protein 4.1); (5760:) synaptojanin 2 binding protein [Homo sapiens]; (5761:) synuclein alpha interacting protein [Homo sapiens]; (5762:) synuclein, gamma (breast cancer-specific protein 1) [Homo sapiens]; (5763:) T cell receptor delta chain [Homo sapiens]; (5764:) tachykinin receptor 1 isoform long [Homo sapiens]; (5765:) tachykinin receptor 1 isoform short [Homo sapiens]; (5766:) TAF2 protein [Homo sapiens]; (5767:) TAF9 RNA polymerase II isoform b [Homo sapiens]; (5768:) TAF9 RNA polymerase II isoform c [Homo sapiens]; (5769:) TAF9 RNA polymerase II, TATA box binding protein (TBP)-associatedfactor, 32kDa [Homo sapiens]; (5770:) talin 1 [Homo sapiens]; (5771:) TANK-binding kinase 1 [Homo sapiens]; (5772:) tartrate resistant acid phosphatase 5 precursor [Homo sapiens]; (5773:) Taste receptor type 1 member 1 precursor (G-protein coupledreceptor 70); (5774:) Taste receptor type 1 member 2 precursor (G-protein coupledreceptor 71) (Sweet taste receptor T1R2); (5775:) Taste receptor type 1 member 3 precursor (Sweet taste receptorT1R3); (5776:) Taste receptor type 2 member 1 (T2R1) (Taste receptor family Bmember 7) (TRB7); (5777:) Taste receptor type 2 member 10 (T2R10) (Taste receptor family Bmember 2) (TRB2); (5778:) Taste receptor type 2 member 13 (T2R13) (Taste receptor family Bmember 3) (TRB3); (5779:) Taste receptor type 2 member 14 (T2R14) (Taste receptor family Bmember 1) (TRB1); (5780:) Taste receptor type 2 member 16 (T2R16); (5781:) Taste receptor type 2 member 3 (T2R3); (5782:) Taste receptor type 2 member 38 (T2R38) (T2R61) (PTC bitter tastereceptor); (5783:) Taste receptor type 2 member 39 (T2R39) (T2R57); (5784:) Taste receptor type 2 member 4 (T2R4); (5785:) Taste receptor type 2 member 40 (T2R40) (T2R58) (G-protein coupledreceptor 60); (5786:) Taste receptor type 2 member 41 (T2R41) (T2R59); (5787:) Taste receptor type 2 member 42 (T2R42) (T2R55); (5788:) Taste receptor type 2 member 43 (T2R43) (T2R52); (5789:) Taste receptor type 2 member 44 (T2R44) (T2R53); (5790:) Taste receptor type 2 member 45 (T2R45) (G-protein coupled receptor59); (5791:) Taste receptor type 2 member 46 (T2R46) (T2R54); (5792:) Taste receptor type 2 member 47 (T2R47); (5793:) Taste receptor type 2 member 48 (T2R48);

(5794:) Taste receptor type 2 member 49 (T2R49) (T2R56); (5795:) Taste receptor type 2 member 5 (T2R5); (5796:) Taste receptor type 2 member 50 (T2R50) (T2R51); (5797:) Taste receptor type 2 member 60 (T2R60) (T2R56); (5798:) Taste receptor type 2 member 7 (T2R7) (Taste receptor family Bmember 4) (TRB4); (5799:) Taste receptor type 2 member 8 (T2R8) (Taste receptor family Bmember 5) (TRB5); (5800:) Taste receptor type 2 member 9 (T2R9) (Taste receptor family Bmember 6) (TRB6); (5801:) TBP-associated factor 1 isoform 1 [Homo sapiens]; (5802:) TBP-associated factor 1 isoform 2 [Homo sapiens]; (5803:) T-cell antigen CD7 precursor (GP40) (T-cell leukemia antigen)(TP41) (Leu-9); (5804:) T-cell receptor alpha chain (clone A21) - human (fragment); (5805:) T-cell receptor alpha chain (Mb11a) precursor - human (fragment); (5806:) T-cell receptor alpha chain C region; (5807:) T-cell receptor alpha chain V region CTL-L17 precursor; (5808:) T-cell receptor alpha chain V region HPB-MLT precursor; (5809:) T-cell receptor alpha chain V region PY14 precursor; (5810:) T-cell receptor beta chain C region; (5811:) T-cell receptor beta chain V region - human (fragment); (5812:) T-cell receptor beta chain V region CTL-L17 precursor; (5813:) T-cell receptor beta chain V region YT35 precursor; (5814:) T-cell receptor gamma chain C region PT-gamma-1/2; (5815:) T-cell receptor gamma chain V region PT-gamma-1/2 precursor; (5816:) T-cell receptor Vb CDR3, carrier PBL Vb 12a.sbt - human(fragment); (5817:) T-cell receptor Vb CDR3, carrier PBL Vb 12b.sbt - human(fragment); (5818:) T-cell receptor Vb CDR3, carrier PBL Vb 2.sbt - human (fragment); (5819:) T-cell receptor Vb CDR3, carrier PBL Vb 6.sbt - human (fragment); (5820:) T-cell receptor Vb CDR3, carrier PBL Vb 7.sbt - human (fragment); (5821:) T-cell receptor Vb CDR3, carrier Vb 17.sbt - human (fragment); (5822:) T-cell receptor Vb CDR3, Ctr1 TCR Vb 12 CDR 3aa.sbt - human(fragment); (5823:) T-cell receptor Vb CDR3, Ctr1 TCR Vb 7CDR 3aas.sbt - human(fragment); (5824:) T-cell receptor Vb CDR3, Ctr1 TCR Vb8 CDR 3aas.sbt - human(fragment); (5825:) T-cell receptor Vb CDR3, Ctr2 TCR Vb12 CDR 3aa.sbt - human(fragment); (5826:) T-cell receptor Vb CDR3, HAM1TCR Vb12b CDR 3a.sbt - human(fragment); (5827:) T-cell receptor Vb CDR3, HAM1TCR Vb14 CDR 3a.sbt - human(fragment); (5828:) T-cell receptor Vb CDR3, HAM1TCR Vb5a CDR 3a.sbt - human(fragment); (5829:) T-cell receptor Vb CDR3, HAM1TCR Vb5b CDR 3a.sbt - human(fragment); (5830:) T-cell receptor Vb CDR3, HAM1TCR Vb5C CDR 3aa.sbt - human(fragment); (5831:) T-cell receptor Vb CDR3, HAM1TCR Vb5d CDR 3a.sbt - human(fragment); (5832:) T-cell receptor Vb CDR3, HAM1TCR Vb6b CDR 3a.sbt - human(fragment); (5833:) T-cell receptor Vb CDR3, HAM1TCR Vb7a CDR 3a.sbt - human(fragment); (5834:) T-cell receptor Vb CDR3, HAM1TCR

Vb7b CDR 3a.sbt - human(fragment); (5835:) T-cell receptor Vb CDR3, HAM1TCR Vb8a CDR 3a.sbt - human(fragment); (5836:) T-cell receptor Vb CDR3, HAM1TCR Vb8b CDR 3a.sbt - human(fragment); (5837:) T-cell receptor Vb CDR3, HAM2TCR Vb 19a.sbt - human (fragment); (5838:) T-cell receptor Vb CDR3, HAM2TCR Vb17 CDR 3a.sbt - human(fragment); (5839:) T-cell receptor Vb CDR3, HAM2TCR Vb19b CDR 3a.sbt - human(fragment); (5840:) T-cell receptor Vb CDR3, HAM2TCR Vb6a CDR 3a.sbt - human(fragment); (5841:) T-cell receptor Vb CDR3, HAM2TCR Vb6b CDR 3a.sbt - human(fragment); (5842:) T-cell receptor Vb CDR3, HAM2TCR Vb8a CDR 3a.sbt - human(fragment); (5843:) T-cell receptor Vb CDR3, HAM2TCR Vb8c CDR 3a.sbt - human(fragment); (5844:) T-cell receptor zeta chain isoform 1 precursor [Homo sapiens]; (5845:) T-cell receptor zeta chain isoform 2 precursor [Homo sapiens]; (5846:) T-cell surface glycoprotein CD3 delta chain precursor (T-cellreceptor T3 delta chain); (5847:) T-cell surface glycoprotein CD3 epsilon chain precursor (T-cellsurface antigen T3/Leu-4 epsilon chain); (5848:) T-cell surface glycoprotein CD3 gamma chain precursor (T-cellreceptor T3 gamma chain); (5849:) T-cell surface glycoprotein CD3 zeta chain precursor (T-cellreceptor T3 zeta chain) (CD237 antigen); (5850:) T-cell, immune regulator 1 isoform a [Homo sapiens]; (5851:) T-cell, immune regulator 1 isoform b [Homo sapiens]; (5852:) TEA domain family member 3 [Homo sapiens]; (5853:) TEK Receptor Tyrosine Kinase Activator; (5854:) Telomerase; (5855:) Telomerase Activator; (5856:) Telomerase reverse transcriptase (Telomerase catalytic subunit)(HEST2) (Telomerase-associated protein 2) (TP2); (5857:) telomerase reverse transcriptase isoform 1 [Homo sapiens]; (5858:) telomerase reverse transcriptase isoform 2 [Homo sapiens]; (5859:) terminal deoxynucleotidyltransferase isoform 1 [Homo sapiens]; (5860:) terminal deoxynucleotidyltransferase isoform 2 [Homo sapiens]; (5861:) testicular ECA [Homo sapiens]; (5862:) testisin isoform 1 [Homo sapiens]; (5863:) testisin isoform 2 [Homo sapiens]; (5864:) testisin isoform 3 [Homo sapiens]; (5865:) Testisin precursor (Eosinophil serine protease 1) (ESP-1); (5866:) Testis-specific serine/threonine-protein kinase 1 (TSSK-1)(Testis-specific kinase 1) (TSK-1) (Serine/threonine-protein kinase22A); (5867:) Testis-specific serine/threonine-protein kinase 2 (TSSK-2)(Testis-specific kinase 2) (TSK-2) (Serine/threonine-protein kinase22B) (DiGeorge syndrome protein G); (5868:) Testis-specific serine/threonine-protein kinase 3 (TSSK-3)(Testis-specific kinase 3) (TSK-3) (Serine/threonine-protein kinase22C); (5869:) Testis-specific serine/threonine-protein kinase 4 (TSSK-4)(Testis-specific kinase 4) (TSK-4) (Serine/threonine-protein kinase22E); (5870:) TGF-beta receptor type III precursor (TGFR-3)

(Transforming growthfactor beta receptor III) (Betaglycan); (5871:) TGF-beta receptor type-1 precursor (TGF-beta receptor type I)(TGFR-1) (TGF-beta type I receptor) (Serine/threonine-proteinkinase receptor R4) (SKR4) (Activin receptor-like kinase 5)(ALK-5); (5872:) TGF-beta receptor type-2 precursor (TGF-beta receptor type II)(TGFR-2) (TGF-beta type II receptor) (Transforming growthfactor-beta receptor type II) (TbetaR-II); (5873:) The Solution Structure Of Reduced Monomeric Superoxide Dismutase,Nmr, 36 Structures; (5874:) thimet oligopeptidase 1 [Homo sapiens]; (5875:) thioesterase II [Homo sapiens]; (5876:) Thiopurine S-methyltransferase (Thiopurine methyltransferase); (5877:) thiopurine S-methyltransferase [Homo sapiens]; (5878:) thioredoxin [Homo sapiens]; (5879:) Thioredoxin domain-containing protein 2 (Spermatid-specificthioredoxin-1) (Sptrx-1); (5880:) Thioredoxin domain-containing protein 6 (Thioredoxin-like protein2) (Txl-2); (5881:) thioredoxin peroxidase [Homo sapiens]; (5882:) Thioredoxin Reductase (TrxR); (5883:) thioredoxin reductase [Homo sapiens]; (5884:) thioredoxin reductase 1 [Homo sapiens]; (5885:) thioredoxin reductase 2 precursor [Homo sapiens]; (5886:) Thioredoxin-1 (Trx-1); (5887:) Thioredoxin-dependent peroxide reductase, mitochondrial precursor(Peroxiredoxin-3) (PRX III) (Antioxidant protein 1) (AOP-1)(Protein MER5 homolog) (HBC189); (5888:) thiosulfate sulfurtransferase [Homo sapiens]; (5889:) Three prime repair exonuclease 1 (3'-5' exonuclease TREX1) (DNaseIII); (5890:) three prime repair exonuclease 1 isoform a [Homo sapiens]; (5891:) three prime repair exonuclease 1 isoform b [Homo sapiens]; (5892:) three prime repair exonuclease 1 isoform c [Homo sapiens]; (5893:) three prime repair exonuclease 1 isoform d [Homo sapiens]; (5894:) three prime repair exonuclease 2 [Homo sapiens]; (5895:) "Threonine aspartase 1 (Taspase-1) [Contains:) Threonine aspartasesubunit alpha; Threonine aspartase subunit beta]."; (5896:) Threonine synthase-like 1 (bacterial) [Homo sapiens]; (5897:) threonine synthase-like 1 [Homo sapiens]; (5898:) Threonine synthase-like 1; (5899:) Thrombin; (5900:) Thrombin Receptor; (5901:) Thrombomodulin precursor (TM) (Fetomodulin) (CD141 antigen); (5902:) Thrombomodulin Receptor; (5903:) Thrombopoietin (TPO) Receptor; (5904:) Thrombopoietin receptor precursor (TPO-R) (Myeloproliferativeleukemia protein) (C-mpl) (CD110 antigen); (5905:) Thrombospondin -1 (TSP-1); (5906:) Thromboxane (TX) Synthesis; (5907:) thromboxane A synthase 1 (platelet, cytochrome P450, family 5,subfamily A) isoform TXS-I [Homo sapiens]; (5908:) thromboxane A synthase 1 (platelet, cytochrome P450, family 5,subfamily A) isoform TXS-II [Homo sapiens]; (5909:) Thromboxane A2 (TXA2) Receptor; (5910:) Thromboxane A2 receptor (TXA2-R) (Prostanoid TP receptor); (5911:) thymidine kinase 1, soluble

[Homo sapiens]; (5912:) thymidine kinase 2 [Homo sapiens]; (5913:) thymidine kinase 2, mitochondrial [Homo sapiens]; (5914:) Thymidine kinase 2, mitochondrial precursor (Mt-TK); (5915:) Thymidine kinase, cytosolic; (5916:) Thymidine Phosphorylase (TP); (5917:) Thymidylate Synthase (TS); (5918:) thymidylate synthetase [Homo sapiens]; (5919:) thymine-DNA glycosylase [Homo sapiens]; (5920:) Thyroid Hormone Receptor (TR); (5921:) Thyroid hormone receptor alpha (C-erbA-alpha) (c-erbA-1) (EAR-7)(EAR7); (5922:) Thyroid hormone receptor beta-1; (5923:) Thyroid hormone receptor beta-2; (5924:) Thyroid hormone receptor-associated protein 2 (Thyroid hormonereceptor-associated protein complex 240 kDa component-like); (5925:) Thyroid hormone receptor-associated protein 3 (Thyroid hormonereceptor-associated protein complex 150 kDa component) (Trap150); (5926:) Thyroid hormone receptor-associated protein complex 240 kDacomponent (Trap240) (Thyroid hormone receptor-associated protein 1)(Vitamin D3 receptor-interacting protein complex component DRIP250)(DRIP 250) (Activator-recruited cofactor 250 kDa component)(ARC250); (5927:) Thyroid Hormone Receptor-Beta (TR Beta); (5928:) Thyroid Peroxidase; (5929:) thyroid peroxidase [Homo sapiens]; (5930:) thyroid peroxidase isoform a [Homo sapiens]; (5931:) thyroid peroxidase isoform b [Homo sapiens]; (5932:) thyroid peroxidase isoform c [Homo sapiens]; (5933:) thyroid peroxidase isoform d [Homo sapiens]; (5934:) thyroid peroxidase isoform e [Homo sapiens]; (5935:) Thyroid peroxidase precursor (TPO); (5936:) Thyroid receptor-interacting protein 12 (TRIP12); (5937:) Thyrotropin receptor precursor (TSH-R) (Thyroid-stimulating hormonereceptor); (5938:) Thyrotropin-Releasing Hormone (TRH) Receptor; (5939:) thyrotropin-releasing hormone degrading enzyme [Homo sapiens]; (5940:) Thyrotropin-releasing hormone receptor (TRH-R) (Thyroliberinreceptor); (5941:) Tie-1 Receptor Tyrosine Kinase; (5942:) TIGD5 protein [Homo sapiens]; (5943:) Tissue alpha-L-fucosidase precursor (Alpha-L-fucosidase I)(Alpha-L-fucoside fucohydrolase); (5944:) Tissue Factor; (5945:) tissue inhibitor of metalloproteinase 1 precursor [Homo sapiens]; (5946:) tissue inhibitor of metalloproteinase 2 precursor [Homo sapiens]; (5947:) tissue inhibitor of metalloproteinase 3 precursor [Homo sapiens]; (5948:) tissue inhibitor of metalloproteinase 4 precursor [Homo sapiens]; (5949:) tissue non-specific alkaline phosphatase precursor [Homo sapiens]; (5950:) Tissue Plasminogen Activator (tPA); (5951:) tissue plasminogen activator (t-PA) [Homo sapiens]; (5952:) "Tissue-type plasminogen activator precursor (tPA) (t-PA)(t-plasminogen activator) (Alteplase) (Reteplase) [Contains:Tissue-type plasminogen activator chain A; Tissue-type plasminogenactivator chain B]."; (5953:) Titin (Connectin)

(Rhabdomyosarcoma antigen MU-RMS-40.14); (5954:) TLL1 protein [Homo sapiens]; (5955:) TLL2 protein [Homo sapiens]; (5956:) T-lymphocyte activation antigen CD80 precursor (Activation B7-1antigen) (CTLA-4 counter-receptor B7.1) (B7) (BB1); (5957:) T-lymphocyte activation antigen CD86 precursor (Activation B7-2antigen) (CTLA-4 counter-receptor B7.2) (B70) (FUN-1) (BU63); (5958:) T-lymphokine-activated killer cell-originated protein kinase (T-LAKcell-originated protein kinase) (PDZ-binding kinase)(Spermatogenesis-related protein kinase) (SPK) (MAPKK-like proteinkinase) (Nori-3); (5959:) TNF receptor-associated factor 2 (Tumor necrosis factor type 2receptor-associated protein 3); (5960:) TNF receptor-associated factor 6 (Interleukin 1 signal transducer)(RING finger protein 85); (5961:) TNF receptor-associated factor 6 [Homo sapiens]; (5962:) TNF-alpha converting enzyme [Homo sapiens]; (5963:) TNF-alpha converting enzyme precursor [Homo sapiens]; (5964:) Toll-Like Receptor (TLR); (5965:) Toll-like receptor 1 precursor (Toll/interleukin-1 receptor-likeprotein) (TIL) (CD281 antigen); (5966:) Toll-like receptor 10 precursor (CD290 antigen); (5967:) Toll-like receptor 2 precursor (Toll/interleukin 1 receptor-likeprotein 4) (CD282 antigen); (5968:) Toll-Like Receptor 3 (TLR3); (5969:) Toll-like receptor 3 precursor (CD283 antigen); (5970:) Toll-Like Receptor 4 (TLR4); (5971:) Toll-like receptor 4 precursor (hToll) (CD284 antigen); (5972:) toll-like receptor 4 precursor [Homo sapiens]; (5973:) Toll-like receptor 5 precursor (Toll/interleukin-1 receptor-likeprotein 3); (5974:) Toll-like receptor 6 precursor; (5975:) Toll-Like Receptor 7 (TLR7); (5976:) Toll-like receptor 7 precursor; (5977:) Toll-like receptor 8 precursor (CD288 antigen); (5978:) Toll-Like Receptor 9 (TLR9); (5979:) Toll-like receptor 9 precursor (CD289 antigen); (5980:) topoisomerase (DNA) III alpha [Homo sapiens]; (5981:) topoisomerase (DNA) III beta [Homo sapiens]; (5982:) Topoisomerase I; (5983:) Topoisomerase II; (5984:) Topoisomerase IV; (5985:) topoisomerase-related function protein [Homo sapiens]; (5986:) TP53-induced glycolysis and apoptosis regulator [Homo sapiens]; (5987:) TPA:) ubiquitin-specific protease 17-like protein [Homo sapiens]; (5988:) TPA_exp:) cytosolic 5'(3')-deoxyribonucleotidase [Homo sapiens]; (5989:) TPK1 protein [Homo sapiens]; (5990:) Trace amine-associated receptor 1 (Trace amine receptor 1) (TaR-1); (5991:) Trace amine-associated receptor 2 (G-protein coupled receptor 58); (5992:) Trace amine-associated receptor 3 (G-protein coupled receptor 57); (5993:) Trace amine-associated receptor 5 (Putative neurotransmitterreceptor); (5994:) Trace amine-associated receptor 6 (Trace amine receptor 4) (TaR-4); (5995:) Trace amine-associated receptor 8 (Trace amine receptor 5) (TaR-5)(G-protein coupled receptor 102); (5996:) Trace amine-associated receptor 9 (Trace amine receptor 3)

(TaR-3); (5997:) TRAF6-regulated IKK activator 1 beta Uev1A [Homo sapiens]; (5998:) Trans-2-enoyl-CoA reductase, mitochondrial precursor (HsNrbf-1)(NRBF-1); (5999:) transacylase [Homo sapiens]; (6000:) transaldolase 1 [Homo sapiens]; (6001:) Transcription elongation factor B (SIII), polypeptide 2 (18kDa,elongin B) [Homo sapiens]; (6002:) Transcription elongation factor B polypeptide 2 (RNA polymerase IItranscription factor SIII subunit B) (SIII p18) (Elongin B) (EloB)(Elongin 18 kDa subunit); (6003:) Transcription elongation factor SPT4 (hSPT4) (DRBsensitivity-inducing factor small subunit) (DSIF small subunit)(DSIF p14); (6004:) Transcription elongation factor SPT5 (hSPT5) (DRBsensitivity-inducing factor large subunit) (DSIF large subunit)(DSIF p160) (Tat-cotransactivator 1 protein) (Tat-CT1 protein); (6005:) transcription factor 1, hepatic [Homo sapiens]; (6006:) transcription factor AP-2 alpha isoform a [Homo sapiens]; (6007:) transcription factor AP-2 alpha isoform b [Homo sapiens]; (6008:) transcription factor AP-2 alpha isoform c [Homo sapiens]; (6009:) transcription factor AP-2 beta (activating enhancer binding protein2 beta) [Homo sapiens]; (6010:) transcription factor AP-2 gamma [Homo sapiens]; (6011:) Transcription factor CP2-like protein 1 (CP2-relatedtranscriptional repressor 1) (CRTR-1) (Transcription factor LBP-9); (6012:) transcription factor LBP-1b [Homo sapiens]; (6013:) transcription factor LBP-9 [Homo sapiens]; (6014:) Transcription factor p65 (Nuclear factor NF-kappa-B p65 subunit); (6015:) transcription factor-like protein 4 isoform alpha [Homo sapiens]; (6016:) transcription factor-like protein 4 isoform beta [Homo sapiens]; (6017:) transcription factor-like protein 4 isoform gamma [Homo sapiens]; (6018:) Transcription initiation factor IIF alpha subunit (TFIIF-alpha)(Transcription initiation factor RAP74) (General transcriptionfactor IIF polypeptide 1 74 kDa subunit protein); (6019:) Transcription initiation factor TFIID subunit 1 (Transcriptioninitiation factor TFIID 250 kDa subunit) (TAF(II)250) (TAFII-250)(TAFII250) (TBP-associated factor 250 kDa) (p250) (Cell cycle gene1 protein); (6020:) Transcriptional repressor NF-X1 (Nuclear transcription factor, Xbox-binding, 1); (6021:) transferrin [Homo sapiens]; (6022:) Transferrin Receptor (Tf-R); (6023:) Transferrin receptor protein 1 (TfR1) (TR) (TfR) (Trfr) (CD71antigen) (T9) (p90); (6024:) Transferrin receptor protein 2 (TfR2); (6025:) Transforming growth factor - beta (TGF- beta); (6026:) Transforming growth factor - beta 1 (TGF- beta 1); (6027:) Transforming growth factor - beta 2 (TGF- beta 2); (6028:) Transforming growth factor alpha (TGF-alpha); (6029:) transforming growth factor, alpha [Homo sapiens]; (6030:) transforming growth factor, beta 1 [Homo sapiens]; (6031:) transforming growth factor, beta receptor II isoform A precursor[Homo sapiens]; (6032:) transforming growth factor, beta

receptor II isoform B precursor[Homo sapiens]; (6033:) Transforming Growth Factor-Beta3 (TGF-Beta3) Receptor; (6034:) Transglutaminase (TGase); (6035:) transglutaminase 1 [Homo sapiens]; (6036:) transglutaminase 2 isoform a [Homo sapiens]; (6037:) transglutaminase 2 isoform b [Homo sapiens]; (6038:) transglutaminase 3 precursor [Homo sapiens]; (6039:) transglutaminase K enzyme; (6040:) Transient receptor potential cation channel subfamily M member 2(Long transient receptor potential channel 2) (LTrpC2) (LTrpC-2)(Transient receptor potential channel 7) (TrpC7)(Estrogen-responsive element-associated gene 1 protein); (6041:) Transketolase (TK); (6042:) transketolase-like 1 [Homo sapiens]; (6043:) translation repressor NAT1 [Homo sapiens]; (6044:) transmembrane 4 superfamily member 15 [Homo sapiens]; (6045:) transmembrane aspartic proteinase Asp 1 [Homo sapiens]; (6046:) transmembrane aspartic proteinase Asp 2 [Homo sapiens]; (6047:) Transmembrane glycoprotein NMB precursor (Transmembraneglycoprotein HGFIN); (6048:) transmembrane protease, serine 11D [Homo sapiens]; (6049:) "Transmembrane protease, serine 11D precursor (Airway trypsin-likeprotease) [Contains:) Transmembrane protease, serine 11Dnon-catalytic chain; Transmembrane protease, serine 11D catalyticchain]."; (6050:) Transmembrane protease, serine 13 (Mosaic serine protease)(Membrane-type mosaic serine protease); (6051:) transmembrane protease, serine 13 [Homo sapiens]; (6052:) "Transmembrane protease, serine 9 (Polyserase-1) (Polyserase-I)(Polyserine protease 1) [Contains:) Serase-1; Serase-2; Serase-3]."; (6053:) trehalase [Homo sapiens]; (6054:) Trem-like transcript 1 protein precursor (TLT-1) (Triggeringreceptor expressed on myeloid cells-like protein 1); (6055:) Trem-like transcript 2 protein precursor (TLT-2) (Triggeringreceptor expressed on myeloid cells-like protein 2); (6056:) TRIAD3 protein isoform a [Homo sapiens]; (6057:) TRIAD3 protein isoform b [Homo sapiens]; (6058:) "Trifunctional enzyme subunit alpha, mitochondrial precursor(TP-alpha) (78 kDa gastrin-binding protein) [Includes:) Long-chainenoyl-CoA hydratase ; Long chain 3-hydroxyacyl-CoA dehydrogenase]."; (6059:) Trifunctional enzyme subunit beta, mitochondrial precursor(TP-beta) [Includes:) 3-ketoacyl-CoA thiolase (Acetyl-CoAacyltransferase) (Beta-ketothiolase)]; (6060:) Triggering receptor expressed on myeloid cells 1 precursor (TREM-1)(Triggering receptor expressed on monocytes 1); (6061:) Triggering receptor expressed on myeloid cells 2 precursor(Triggering receptor expressed on monocytes 2) (TREM-2); (6062:) Triggering Receptor Expressed on Myeloid Cells-1 (TREM-1) Receptor; (6063:) Trimethyllysine dioxygenase, mitochondrial precursor(Epsilon-trimethyllysine 2-oxoglutarate dioxygenase)(TML-alpha-

ketoglutarate dioxygenase) (TML hydroxylase) (TMLdioxygenase) (TMLD); (6064:) trimethyllysine hydroxylase, epsilon [Homo sapiens]; (6065:) Triosephosphate isomerase (TIM) (Triose-phosphate isomerase); (6066:) triosephosphate isomerase 1 [Homo sapiens]; (6067:) tripeptidyl peptidase II [Homo sapiens]; (6068:) tripeptidyl peptidase II; (6069:) Tripeptidyl-peptidase 2 (Tripeptidyl-peptidase II) (TPP-II)(Tripeptidyl aminopeptidase); (6070:) tripeptidyl-peptidase I precursor [Homo sapiens]; (6071:) tRNA 5-methylaminomethyl-2-thiouridylate methyltransferase 1 [Homosapiens]; (6072:) tRNA isopentenyl transferase [Homo sapiens]; (6073:) tRNA isopentenyltransferase 1 [Homo sapiens]; (6074:) tRNA isopentenyltransferase, mitochondrial precursor(Isopentenyl-diphosphate:tRNA isopentenyltransferase) (IPPtransferase) (IPTase) (IPPT) (hGRO1); (6075:) tRNA nucleotidyl transferase, CCA-adding, 1 isoform 1 [Homosapiens]; (6076:) tRNA nucleotidyl transferase, CCA-adding, 1 isoform 2 [Homosapiens]; (6077:) tRNA-guanine transglycosylase [Homo sapiens]; (6078:) tRNA-nucleotidyltransferase [Homo sapiens]; (6079:) tRNA-nucleotidyltransferase 1, mitochondrial precursor(Mitochondrial tRNA nucleotidyl transferase, CCA-adding) (mt tRNAadenylyltransferase) (mt tRNA CCA-pyrophosphorylase) (mt tRNACCA-diphosphorylase) (mt CCA-adding enzyme); (6080:) truncated mercaptopyruvate sulfurtransferase variant [Homosapiens]; (6081:) Trypanosoma Cruzi Trypanothione Reductase; (6082:) Trypsin; (6083:) Tryptase; (6084:) Tryptase Beta; (6085:) Tryptase delta precursor (Delta tryptase) (Mast cell mMCP-7-like)(Tryptase-3) (HmMCP-3-like tryptase III); (6086:) tryptophan hydroxylase 1 [Homo sapiens]; (6087:) tryptophanyl-tRNA synthetase isoform a [Homo sapiens]; (6088:) tryptophanyl-tRNA synthetase isoform b [Homo sapiens]; (6089:) TTLL3 protein [Homo sapiens]; (6090:) T-Type Calcium Channel (CaV3.1d) Blocker; (6091:) Tubulin; (6092:) Tubulin Polymerase; (6093:) tubulin tyrosine ligase [Homo sapiens]; (6094:) Tumor Necrosis Apoptosis Inducing Ligand Receptor 1 (TRAIL-R1); (6095:) Tumor Necrosis Apoptosis Inducing Ligand Receptor 2 (TRAIL-R2); (6096:) Tumor Necrosis Factor (TNF) Release; (6097:) tumor necrosis factor alpha [Homo sapiens]; (6098:) "Tumor necrosis factor ligand superfamily member 11 (Receptoractivator of nuclear factor kappa B ligand) (RANKL) (TNF-relatedactivation-induced cytokine) (TRANCE) (Osteoprotegerin ligand)(OPGL) (Osteoclast differentiation factor) (ODF) (CD254 antigen)[Contains:) Tumor necrosis factor ligand superfamily member 11,membrane form; Tumor necrosis factor ligand superfamily member 11,soluble form]."; (6099:) tumor necrosis factor ligand superfamily, member 11 isoform 1 [Homosapiens]; (6100:) tumor necrosis factor ligand superfamily, member 11 isoform 2 [Homosapiens]; (6101:) Tumor Necrosis

Factor Receptor 1 (TNFR1); (6102:) tumor necrosis factor receptor 1 precursor [Homo sapiens]; (6103:) Tumor necrosis factor receptor superfamily member 10A precursor(Death receptor 4) (TNF-related apoptosis-inducing ligand receptor1) (TRAIL receptor 1) (TRAIL-R1) (CD261 antigen); (6104:) Tumor necrosis factor receptor superfamily member 10B precursor(Death receptor 5) (TNF-related apoptosis-inducing ligand receptor2) (TRAIL receptor 2) (TRAIL-R2) (CD262 antigen); (6105:) Tumor necrosis factor receptor superfamily member 10C precursor(Decoy receptor 1) (DcR1) (Decoy TRAIL receptor without deathdomain) (TNF-related apoptosis-inducing ligand receptor 3) (TRAILreceptor 3) (TRAIL-R3) (Trail receptor without an intracellulardomain) (Lymphocyte inhibitor of TRAIL) (Antagonist decoy receptorfor TRAIL/Apo-2L) (CD263 antigen); (6106:) Tumor necrosis factor receptor superfamily member 10D precursor(Decoy receptor 2) (DcR2) (TNF-related apoptosis-inducing ligandreceptor 4) (TRAIL receptor 4) (TRAIL-R4) (TRAIL receptor with atruncated death domain) (CD264 antigen); (6107:) Tumor necrosis factor receptor superfamily member 11A precursor(Receptor activator of NF-KB) (Osteoclast differentiation factorreceptor) (ODFR) (CD265 antigen); (6108:) Tumor necrosis factor receptor superfamily member 11B precursor(Osteoprotegerin) (Osteoclastogenesis inhibitory factor); (6109:) Tumor necrosis factor receptor superfamily member 12A precursor(Fibroblast growth factor-inducible immediate-early responseprotein 14) (FGF-inducible 14) (Tweak-receptor) (TweakR) (CD266antigen); (6110:) Tumor necrosis factor receptor superfamily member 13B(Transmembrane activator and CAML interactor) (CD267 antigen); (6111:) Tumor necrosis factor receptor superfamily member 13C (Bcell-activating factor receptor) (BAFF receptor) (BAFF-R) (BLySreceptor 3) (CD268 antigen); (6112:) Tumor necrosis factor receptor superfamily member 14 precursor(Herpesvirus entry mediator A) (Tumor necrosis factor receptor-like2) (TR2); (6113:) Tumor necrosis factor receptor superfamily member 16 precursor(Low-affinity nerve growth factor receptor) (NGF receptor)(Gp80-LNGFR) (p75 ICD) (Low affinity neurotrophin receptor p75NTR)(CD271 antigen); (6114:) Tumor necrosis factor receptor superfamily member 17 (B-cellmaturation protein) (CD269 antigen); (6115:) Tumor necrosis factor receptor superfamily member 18 precursor(Glucocorticoid-induced TNFR-related protein) (Activation-inducibleTNFR family receptor); (6116:) Tumor necrosis factor receptor superfamily member 19 precursor(Toxicity and JNK inducer) (TRADE); (6117:) Tumor necrosis factor receptor superfamily member 19L precursor(Receptor expressed in lymphoid tissues); (6118:) "Tumor necrosis factor receptor superfamily member 1A

precursor(p60) (TNF-R1) (TNF-RI) (TNFR-I) (p55) (CD120a antigen) [Contains:Tumor necrosis factor receptor superfamily member 1A, membraneform; Tumor necrosis factor-binding protein 1 (TBPI)]."; (6119:) "Tumor necrosis factor receptor superfamily member 1B precursor(Tumor necrosis factor receptor 2) (TNF-R2) (Tumor necrosis factorreceptor type II) (p75) (p80 TNF-alpha receptor) (CD120b antigen)(Etanercept) [Contains:) Tumor necrosis factor receptor superfamilymember 1b, membrane form; Tumor necrosis factor-binding protein 2(TBPII) (TBP-2)]."; (6120:) Tumor necrosis factor receptor superfamily member 21 precursor(TNFR-related death receptor 6) (Death receptor 6); (6121:) Tumor necrosis factor receptor superfamily member 25 precursor(WSL-1 protein) (Apoptosis-mediating receptor DR3)(Apoptosis-mediating receptor TRAMP) (Death domain receptor 3) (WSLprotein) (Apoptosis-inducing receptor AIR) (Apo-3)(Lymphocyte-associated receptor of death) (LARD); (6122:) Tumor necrosis factor receptor superfamily member 27 (X-linkedectodysplasin-A2 receptor) (EDA-A2 receptor); (6123:) Tumor necrosis factor receptor superfamily member 3 precursor(Lymphotoxin-beta receptor) (Tumor necrosis factor receptor2-related protein) (Tumor necrosis factor C receptor); (6124:) Tumor necrosis factor receptor superfamily member 4 precursor(OX40L receptor) (ACT35 antigen) (TAX transcriptionally-activatedglycoprotein 1 receptor) (CD134 antigen); (6125:) Tumor necrosis factor receptor superfamily member 5 precursor(CD40L receptor) (B-cell surface antigen CD40) (CDw40) (Bp50); (6126:) Tumor necrosis factor receptor superfamily member 6 precursor(FASLG receptor) (Apoptosis-mediating surface antigen FAS) (Apo-1antigen) (CD95 antigen); (6127:) Tumor necrosis factor receptor superfamily member 6B precursor(Decoy receptor for Fas ligand) (Decoy receptor 3) (DcR3) (M68); (6128:) Tumor necrosis factor receptor superfamily member 7 precursor(CD27L receptor) (T-cell activation antigen CD27) (T14); (6129:) Tumor necrosis factor receptor superfamily member 8 precursor(CD30L receptor) (Lymphocyte activation antigen CD30) (KI-1antigen); (6130:) Tumor necrosis factor receptor superfamily member 9 precursor(4-1BB ligand receptor) (T-cell antigen 4-1BB homolog) (T-cellantigen ILA) (CD137 antigen) (CDw137); (6131:) Tumor necrosis factor receptor superfamily member EDAR precursor(Anhidrotic ectodysplasin receptor 1) (Ectodysplasin-A receptor)(EDA-A1 receptor) (Ectodermal dysplasia receptor) (Downlesshomolog); (6132:) tumor necrosis factor receptor superfamily, member 6 isoform 1precursor [Homo sapiens]; (6133:) tumor necrosis factor receptor superfamily, member 6 isoform 2precursor [Homo sapiens]; (6134:) tumor necrosis factor receptor superfamily, member 6 isoform 3precursor [Homo

sapiens]; (6135:) tumor necrosis factor receptor superfamily, member 6 isoform 4precursor [Homo sapiens]; (6136:) tumor necrosis factor receptor superfamily, member 6 isoform 5precursor [Homo sapiens]; (6137:) tumor necrosis factor receptor superfamily, member 6 isoform 6precursor [Homo sapiens]; (6138:) tumor necrosis factor receptor superfamily, member 6 isoform 7precursor [Homo sapiens]; (6139:) tumor necrosis factor receptor superfamily, member 8 isoform 1precursor [Homo sapiens]; (6140:) tumor necrosis factor receptor superfamily, member 8 isoform 2[Homo sapiens]; (6141:) tumor necrosis factor, alpha-induced protein 8 isoform a [Homosapiens]; (6142:) tumor necrosis factor, alpha-induced protein 8 isoform b [Homosapiens]; (6143:) Tumor Necrosis Factor-Alpha (TNF-Alpha) Synthesis; (6144:) Tumor Necrosis Factor-Alpha Converting Enzyme (TACE); (6145:) tumor protein p53 [Homo sapiens]; (6146:) tumor stroma and activated macrophage protein DLM-1 [Homo sapiens]; (6147:) Tumor susceptibility gene 101 protein; (6148:) "Tumor-associated hydroquinone oxidase (tNOX) (Cytosolic ovariancarcinoma antigen 1) (APK1 antigen) [Includes:) Hydroquinone [NADH]oxidase ; Protein disulfide-thiol oxidoreductase]."; (6149:) Tumour Cell Survival Phosphatase-1 (TCSP-1); (6150:) TX protease precursor [Homo sapiens]; (6151:) TY protease [Homo sapiens]; (6152:) Type II inositol-3,4-bisphosphate 4-phosphatase (Inositolpolyphosphate 4-phosphatase type II); (6153:) Type-1 angiotensin II receptor (AT1) (AT1AR) (AT1BR); (6154:) Type-2 angiotensin II receptor (AT2); (6155:) Tyrosinase; (6156:) Tyrosinase precursor (Monophenol monooxygenase) (Tumor rejectionantigen AB) (SK29-AB) (LB24-AB); (6157:) tyrosinase precursor [Homo sapiens]; (6158:) tyrosine 3/tryptophan 5 -monooxygenase activation protein, thetapolypeptide [Homo sapiens]; (6159:) tyrosine 3/tryptophan 5 -monooxygenase activation protein, zetapolypeptide [Homo sapiens]; (6160:) Tyrosine 3-monooxygenase (Tyrosine 3-hydroxylase) (TH); (6161:) tyrosine hydroxylase isoform a [Homo sapiens]; (6162:) tyrosine hydroxylase isoform b [Homo sapiens]; (6163:) tyrosine hydroxylase isoform c [Homo sapiens]; (6164:) Tyrosine Kinase; (6165:) Tyrosine-protein kinase 6 (Breast tumor kinase) (Tyrosine-proteinkinase BRK); (6166:) Tyrosine-protein kinase receptor Tie-1 precursor; (6167:) Tyrosine-protein kinase receptor TYRO3 precursor (Tyrosine-proteinkinase RSE) (Tyrosine-protein kinase SKY) (Tyrosine-protein kinaseDTK) (Protein-tyrosine kinase byk); (6168:) Tyrosine-protein kinase receptor UFO precursor (AXL oncogene); (6169:) Tyrosine-protein kinase RYK precursor; (6170:) Tyrosine-protein kinase transmembrane receptor ROR1 precursor(Neurotrophic tyrosine kinase, receptor-related 1); (6171:) Tyrosine-protein kinase transmembrane

receptor ROR2 precursor(Neurotrophic tyrosine kinase, receptor-related 2); (6172:) Tyrosine-protein kinase-like 7 precursor (Colon carcinoma kinase 4)(CCK-4); (6173:) Tyrosine-protein phosphatase non-receptor type 11 (Protein-tyrosinephosphatase 2C) (PTP-2C) (PTP-1D) (SH-PTP3) (SH-PTP2) (SHP-2)(Shp2); (6174:) Tyrosyl-DNA phosphodiesterase 1 (Tyr-DNA phosphodiesterase 1); (6175:) tyrosyl-DNA phosphodiesterase 1 [Homo sapiens]; (6176:) tyrosylprotein sulfotransferase 1 [Homo sapiens]; (6177:) tyrosylprotein sulfotransferase-1 [Homo sapiens]; (6178:) tyrosylprotein sulfotransferase-2 [Homo sapiens]; (6179:) "tyrosylprotein sulfotransferase-2; TPST-2 [Homo sapiens]."; (6180:) tyrosyl-tRNA synthetase [Homo sapiens]; (6181:) UBA2 [Homo sapiens]; (6182:) UBA3 [Homo sapiens]; (6183:) UBC13/UEV-interacting ring finger protein [Homo sapiens]; (6184:) Ubc6p homolog [Homo sapiens]; (6185:) UbcH5B; (6186:) UbcH5C; (6187:) UbcM2 [Homo sapiens]; (6188:) UBE1C [Homo sapiens]; (6189:) UBE1L protein [Homo sapiens]; (6190:) UBE1L2 protein [Homo sapiens]; (6191:) UBE21 [Homo sapiens]; (6192:) UBE2B [Homo sapiens]; (6193:) UBE2C [Homo sapiens]; (6194:) UBE2D3 [Homo sapiens]; (6195:) UBE2G1 protein [Homo sapiens]; (6196:) UBE2H protein [Homo sapiens]; (6197:) UBE2I protein [Homo sapiens]; (6198:) UBE2L3 [Homo sapiens]; (6199:) UBE2L6 [Homo sapiens]; (6200:) UBE2O protein [Homo sapiens]; (6201:) UBE2Q [Homo sapiens]; (6202:) UBE2Q1 protein [Homo sapiens]; (6203:) UBE2Q2 protein [Homo sapiens]; (6204:) UBE2R2 [Homo sapiens]; (6205:) UBE2S protein [Homo sapiens]; (6206:) UBE2V1 protein [Homo sapiens]; (6207:) UBE2V2 [Homo sapiens]; (6208:) UBE2W protein [Homo sapiens]; (6209:) UBE2Z protein [Homo sapiens]; (6210:) ubenimex (Bestatin)-sensitive aminopeptidase B-like enzyme (EC3.4.11.-) - human (fragments); (6211:) ubiquinol-cytochrome-c reductase (EC 1.10.2.2) cytochrome b - humanmitochondrion; (6212:) Ubiquitin activating enzyme [Homo sapiens]; (6213:) ubiquitin activating enzyme E1 [Homo sapiens]; (6214:) ubiquitin associated protein 2 [Homo sapiens]; (6215:) ubiquitin B precursor [Homo sapiens]; (6216:) ubiquitin carboxyl-terminal esterase L1 (ubiquitin thiolesterase)[Homo sapiens]; (6217:) ubiquitin carboxyl-terminal esterase L3 [Homo sapiens]; (6218:) Ubiquitin carboxyl-terminal hydrolase 1 (Ubiquitin thioesterase 1)(Ubiquitin-specific-processing protease 1) (Deubiquitinating enzyme1) (hUBP); (6219:) Ubiquitin carboxyl-terminal hydrolase 10 (Ubiquitin thioesterase10) (Ubiquitin-specific-processing protease 10) (Deubiquitinatingenzyme 10); (6220:) Ubiquitin carboxyl-terminal hydrolase 11 (Ubiquitin thioesterase11) (Ubiquitin-specific-processing protease 11) (Deubiquitinatingenzyme 11); (6221:) Ubiquitin carboxyl-terminal hydrolase 12 (Ubiquitin thioesterase12) (Ubiquitin-specific-

processing protease 12) (Deubiquitinatingenzyme 12) (Ubiquitin-hydrolyzing enzyme 1); (6222:) Ubiquitin carboxyl-terminal hydrolase 13 (Ubiquitin thioesterase13) (Ubiquitin-specific-processing protease 13) (Deubiquitinatingenzyme 13) (Isopeptidase T-3) (ISOT-3); (6223:) Ubiquitin carboxyl-terminal hydrolase 14 (Ubiquitin thioesterase14) (Ubiquitin-specific-processing protease 14) (Deubiquitinatingenzyme 14); (6224:) Ubiquitin carboxyl-terminal hydrolase 15 (Ubiquitin thioesterase15) (Ubiquitin-specific-processing protease 15) (Deubiquitinatingenzyme 15) (Unph-2) (Unph4); (6225:) Ubiquitin carboxyl-terminal hydrolase 16 (Ubiquitin thioesterase16) (Ubiquitin-specific-processing protease 16) (Deubiquitinatingenzyme 16) (Ubiquitin-processing protease UBP-M); (6226:) Ubiquitin carboxyl-terminal hydrolase 17-like protein (Ubiquitinthioesterase 17-like) (Ubiquitin-specific-processing protease17-like) (Deubiquitinating enzyme 17-like); (6227:) Ubiquitin carboxyl-terminal hydrolase 19 (Ubiquitin thioesterase19) (Ubiquitin-specific-processing protease 19) (Deubiquitinatingenzyme 19) (Zinc finger MYND domain-containing protein 9); (6228:) Ubiquitin carboxyl-terminal hydrolase 2 (Ubiquitin thioesterase 2)(Ubiquitin-specific-processing protease 2) (Deubiquitinating enzyme2) (41 kDa ubiquitin-specific protease); (6229:) Ubiquitin carboxyl-terminal hydrolase 20 (Ubiquitin thioesterase20) (Ubiquitin-specific-processing protease 20) (Deubiquitinatingenzyme 20); (6230:) Ubiquitin carboxyl-terminal hydrolase 21 (Ubiquitin thioesterase21) (Ubiquitin-specific-processing protease 21) (Deubiquitinatingenzyme 21) (NEDD8-specific protease); (6231:) Ubiquitin carboxyl-terminal hydrolase 22 (Ubiquitin thioesterase22) (Ubiquitin-specific-processing protease 22) (Deubiquitinatingenzyme 22); (6232:) Ubiquitin carboxyl-terminal hydrolase 24 (Ubiquitin thioesterase24) (Ubiquitin-specific-processing protease 24) (Deubiquitinatingenzyme 24); (6233:) Ubiquitin carboxyl-terminal hydrolase 25 (Ubiquitin thioesterase25) (Ubiquitin-specific-processing protease 25) (Deubiquitinatingenzyme 25) (USP on chromosome 21); (6234:) Ubiquitin carboxyl-terminal hydrolase 26 (Ubiquitin thioesterase26) (Ubiquitin-specific-processing protease 26) (Deubiquitinatingenzyme 26); (6235:) Ubiquitin carboxyl-terminal hydrolase 28 (Ubiquitin thioesterase28) (Ubiquitin-specific-processing protease 28) (Deubiquitinatingenzyme 28); (6236:) Ubiquitin carboxyl-terminal hydrolase 29 (Ubiquitin thioesterase29) (Ubiquitin-specific-processing protease 29) (Deubiquitinatingenzyme 29); (6237:) Ubiquitin carboxyl-terminal hydrolase 3 (Ubiquitin thioesterase 3)(Ubiquitin-specific-processing protease 3) (Deubiquitinating enzyme3); (6238:) Ubiquitin carboxyl-terminal hydrolase 30 (Ubiquitin

thioesterase30) (Ubiquitin-specific-processing protease 30) (Deubiquitinatingenzyme 30); (6239:) Ubiquitin carboxyl-terminal hydrolase 31 (Ubiquitin thioesterase31) (Ubiquitin-specific-processing protease 31) (Deubiquitinatingenzyme 31); (6240:) Ubiquitin carboxyl-terminal hydrolase 32 (Ubiquitin thioesterase32) (Ubiquitin-specific-processing protease 32) (Deubiquitinatingenzyme 32) (NY-REN-60 antigen); (6241:) Ubiquitin carboxyl-terminal hydrolase 33 (Ubiquitin thioesterase33) (Ubiquitin-specific-processing protease 33) (Deubiquitinatingenzyme 33) (VHL-interacting deubiquitinating enzyme 1); (6242:) Ubiquitin carboxyl-terminal hydrolase 34 (Ubiquitin thioesterase34) (Ubiquitin-specific-processing protease 34) (Deubiquitinatingenzyme 34); (6243:) Ubiquitin carboxyl-terminal hydrolase 35 (Ubiquitin thioesterase35) (Ubiquitin-specific-processing protease 35) (Deubiquitinatingenzyme 35); (6244:) Ubiquitin carboxyl-terminal hydrolase 36 (Ubiquitin thioesterase36) (Ubiquitin-specific-processing protease 36) (Deubiquitinatingenzyme 36); (6245:) Ubiquitin carboxyl-terminal hydrolase 37 (Ubiquitin thioesterase37) (Ubiquitin-specific-processing protease 37) (Deubiquitinatingenzyme 37); (6246:) Ubiquitin carboxyl-terminal hydrolase 38 (Ubiquitin thioesterase38) (Ubiquitin-specific-processing protease 38) (Deubiquitinatingenzyme 38) (HP43.8KD); (6247:) Ubiquitin carboxyl-terminal hydrolase 4 (Ubiquitin thioesterase 4)(Ubiquitin-specific-processing protease 4) (Deubiquitinating enzyme4) (Ubiquitous nuclear protein homolog); (6248:) Ubiquitin carboxyl-terminal hydrolase 40 (Ubiquitin thioesterase40) (Ubiquitin-specific-processing protease 40) (Deubiquitinatingenzyme 40); (6249:) Ubiquitin carboxyl-terminal hydrolase 42 (Ubiquitin thioesterase42) (Ubiquitin-specific-processing protease 42) (Deubiquitinatingenzyme 42); (6250:) Ubiquitin carboxyl-terminal hydrolase 43 (Ubiquitin thioesterase43) (Ubiquitin-specific-processing protease 43) (Deubiquitinatingenzyme 43); (6251:) Ubiquitin carboxyl-terminal hydrolase 44 (Ubiquitin thioesterase44) (Ubiquitin-specific-processing protease 44) (Deubiquitinatingenzyme 44); (6252:) Ubiquitin carboxyl-terminal hydrolase 46 (Ubiquitin thioesterase46) (Ubiquitin-specific-processing protease 46) (Deubiquitinatingenzyme 46); (6253:) Ubiquitin carboxyl-terminal hydrolase 47 (Ubiquitin thioesterase47) (Ubiquitin-specific-processing protease 47) (Deubiquitinatingenzyme 47); (6254:) Ubiquitin carboxyl-terminal hydrolase 48 (Ubiquitin thioesterase48) (Ubiquitin-specific-processing protease 48) (Deubiquitinatingenzyme 48); (6255:) Ubiquitin carboxyl-terminal hydrolase 49 (Ubiquitin thioesterase49) (Ubiquitin-specific-processing protease 49) (Deubiquitinatingenzyme 49); (6256:) Ubiquitin carboxyl-terminal hydrolase 5

(Ubiquitin thioesterase 5)(Ubiquitin-specific-processing protease 5) (Deubiquitinating enzyme5) (Isopeptidase T); (6257:) Ubiquitin carboxyl-terminal hydrolase 51 (Ubiquitin thioesterase51) (Ubiquitin-specific-processing protease 51) (Deubiquitinatingenzyme 51); (6258:) Ubiquitin carboxyl-terminal hydrolase 6 (Ubiquitin thioesterase 6)(Ubiquitin-specific-processing protease 6) (Deubiquitinating enzyme6) (Proto-oncogene TRE-2); (6259:) Ubiquitin carboxyl-terminal hydrolase 7 (Ubiquitin thioesterase 7)(Ubiquitin-specific-processing protease 7) (Deubiquitinating enzyme7) (Herpesvirus-associated ubiquitin-specific protease); (6260:) Ubiquitin carboxyl-terminal hydrolase 8 (Ubiquitin thioesterase 8)(Ubiquitin-specific-processing protease 8) (Deubiquitinating enzyme8) (hUBPy); (6261:) Ubiquitin carboxyl-terminal hydrolase BAP1 (BRCA1-associatedprotein 1) (Cerebral protein 6); (6262:) ubiquitin carboxyl-terminal hydrolase CYLD isoform 1 [Homosapiens]; (6263:) ubiquitin carboxyl-terminal hydrolase CYLD isoform 2 [Homosapiens]; (6264:) Ubiquitin carboxyl-terminal hydrolase isozyme L1 (UCH-L1)(Ubiquitin thioesterase L1) (Neuron cytoplasmic protein 9.5) (PGP9.5) (PGP9.5); (6265:) Ubiquitin carboxyl-terminal hydrolase isozyme L3 (UCH-L3)(Ubiquitin thioesterase L3); (6266:) Ubiquitin carboxyl-terminal hydrolase isozyme L5 (UCH-L5)(Ubiquitin thioesterase L5) (Ubiquitin C-terminal hydrolase UCH37); (6267:) ubiquitin carrier protein [Homo sapiens]; (6268:) ubiquitin carrier protein E2 - human; (6269:) ubiquitin carrier protein; (6270:) ubiquitin conjugating enzyme - human (fragment); (6271:) ubiquitin conjugating enzyme [Homo sapiens]; (6272:) ubiquitin conjugating enzyme 12 [Homo sapiens]; (6273:) ubiquitin conjugating enzyme 6 [Homo sapiens]; (6274:) ubiquitin conjugating enzyme 7 interacting protein 5 isoform avariant [Homo sapiens]; (6275:) ubiquitin conjugating enzyme 7 interacting protein 5 isoform bvariant [Homo sapiens]; (6276:) ubiquitin conjugating enzyme 9 [Homo sapiens]; (6277:) ubiquitin conjugating enzyme 9; (6278:) ubiquitin conjugating enzyme E2 [Homo sapiens]; (6279:) ubiquitin conjugating enzyme E2, J2 isoform 1 [Homo sapiens]; (6280:) ubiquitin conjugating enzyme E2, J2 isoform 2 [Homo sapiens]; (6281:) ubiquitin conjugating enzyme E2, J2 isoform 3 [Homo sapiens]; (6282:) ubiquitin conjugating enzyme G2 [Homo sapiens]; (6283:) ubiquitin conjugating enzyme homolog; (6284:) ubiquitin conjugating enzyme; (6285:) ubiquitin C-terminal hydrolase UCH37 [Homo sapiens]; (6286:) ubiquitin hydrolyzing enzyme 1 [Homo sapiens]; (6287:) ubiquitin hydrolyzing enzyme I [Homo sapiens]; (6288:) Ubiquitin isopeptidase T [Homo sapiens]; (6289:) Ubiquitin Ligase; (6290:) ubiquitin ligase E3A isoform 1 [Homo sapiens]; (6291:) Ubiquitin ligase LNX (Numb-binding protein 1) (Ligand ofNumb-protein X 1); (6292:) Ubiquitin ligase protein DZIP3 (DAZ-

interacting protein 3)(RNA-binding ubiquitin ligase of 138 kDa) (hRUL138); (6293:) Ubiquitin ligase protein RING2 (RING finger protein 2) (RING fingerprotein 1B) (RING1b) (RING finger protein BAP-1) (DinG protein)(Huntingtin-interacting protein 2-interacting protein 3)(HIP2-interacting protein 3); (6294:) Ubiquitin ligase SIAH1 (Seven in absentia homolog 1) (Siah-1)(Siah-1a); (6295:) Ubiquitin ligase SIAH2 (Seven in absentia homolog 2) (Siah-2)(hSiah2); (6296:) ubiquitin processing protease [Homo sapiens]; (6297:) ubiquitin protein ligase E3A isoform 1 [Homo sapiens]; (6298:) ubiquitin protein ligase E3A isoform 2 [Homo sapiens]; (6299:) ubiquitin protein ligase E3A isoform 3 [Homo sapiens]; (6300:) ubiquitin protein ligase E3B [Homo sapiens]; (6301:) ubiquitin protein ligase E3C [Homo sapiens]; (6302:) Ubiquitin protein ligase Praja1 (RING finger protein 70); (6303:) ubiquitin specific protease 1 [Homo sapiens]; (6304:) ubiquitin specific protease 11 [Homo sapiens]; (6305:) ubiquitin specific protease 14 isoform a [Homo sapiens]; (6306:) ubiquitin specific protease 14 isoform b [Homo sapiens]; (6307:) ubiquitin specific protease 15 [Homo sapiens]; (6308:) ubiquitin specific protease 16 isoform a [Homo sapiens]; (6309:) ubiquitin specific protease 16 isoform b [Homo sapiens]; (6310:) ubiquitin specific protease 2 isoform b [Homo sapiens]; (6311:) ubiquitin specific protease 20 [Homo sapiens]; (6312:) ubiquitin specific protease 25 [Homo sapiens]; (6313:) ubiquitin specific protease 28 [Homo sapiens]; (6314:) ubiquitin specific protease 29 [Homo sapiens]; (6315:) ubiquitin specific protease 2b [Homo sapiens]; (6316:) ubiquitin specific protease 31 [Homo sapiens]; (6317:) ubiquitin specific protease 33 isoform 1 [Homo sapiens]; (6318:) ubiquitin specific protease 33 isoform 2 [Homo sapiens]; (6319:) ubiquitin specific protease 33 isoform 3 [Homo sapiens]; (6320:) ubiquitin specific protease 36 [Homo sapiens]; (6321:) ubiquitin specific protease 42 [Homo sapiens]; (6322:) ubiquitin specific protease 48 [Homo sapiens]; (6323:) ubiquitin specific protease 48 isoform a [Homo sapiens]; (6324:) ubiquitin specific protease 51 [Homo sapiens]; (6325:) ubiquitin specific protease 7 (herpes virus-associated) [Homosapiens]; (6326:) ubiquitin specific protease 8 [Homo sapiens]; (6327:) ubiquitin specific protease 9, X-linked isoform 3 [Homo sapiens]; (6328:) ubiquitin specific protease 9, X-linked isoform 4 [Homo sapiens]; (6329:) ubiquitin specific protease 9, Y-linked [Homo sapiens]; (6330:) ubiquitin specific protease, proto-oncogene isoform a [Homosapiens]; (6331:) ubiquitin specific protease, proto-oncogene isoform b [Homosapiens]; (6332:) Ubiquitin thioesterase protein OTUB1 (Otubain-1) (OTUdomain-containing ubiquitin aldehyde-binding protein 1)(Ubiquitin-specific-processing protease OTUB1) (Deubiquitinatingenzyme OTUB1); (6333:) Ubiquitin thioesterase protein OTUB2 (Otubain-2) (OTUdomain-

containing ubiquitin aldehyde-binding protein 2)(Ubiquitin-specific-processing protease OTUB2) (Deubiquitinatingenzyme OTUB2); (6334:) Ubiquitin; (6335:) Ubiquitin-activating enzyme E1 (A1S9 protein); (6336:) Ubiquitin-activating enzyme E1 (A1S9T and BN75 temperaturesensitivity complementing) [Homo sapiens]; (6337:) ubiquitin-activating enzyme E1 [Homo sapiens]; (6338:) Ubiquitin-activating enzyme E1 domain-containing protein 1(UFM1-activating enzyme) (Ubiquitin-activating enzyme 5) (ThiFP1); (6339:) Ubiquitin-activating enzyme E1 homolog (D8); (6340:) Ubiquitin-activating enzyme E1C (UBA3 homolog, yeast) [Homosapiens]; (6341:) ubiquitin-activating enzyme E1C isoform 1 [Homo sapiens]; (6342:) ubiquitin-activating enzyme E1C isoform 2 [Homo sapiens]; (6343:) ubiquitin-activating enzyme E1C isoform 3 [Homo sapiens]; (6344:) Ubiquitin-activating enzyme E1-domain containing 1 [Homo sapiens]; (6345:) ubiquitin-activating enzyme E1-domain containing 1 isoform 1 [Homosapiens]; (6346:) ubiquitin-activating enzyme E1-domain containing 1 isoform 2 [Homosapiens]; (6347:) ubiquitin-activating enzyme E1-like [Homo sapiens]; (6348:) Ubiquitin-activating enzyme E1-like 2 [Homo sapiens]; (6349:) ubiquitin-activating enzyme E1-related protein; (6350:) ubiquitination factor E4A [Homo sapiens]; (6351:) ubiquitin-coniugating enzyme [Homo sapiens]; (6352:) ubiquitin-conjugating BIR-domain enzyme APOLLON [Homo sapiens]; (6353:) ubiquitin-conjugating enzyme [Homo sapiens]; (6354:) ubiquitin-conjugating enzyme 1 isoform [Homo sapiens]; (6355:) ubiquitin-conjugating enzyme 16 [Homo sapiens]; (6356:) Ubiquitin-conjugating enzyme 7-interacting protein 4(UbcM4-interacting protein 4) (RING finger protein 144); (6357:) ubiquitin-conjugating enzyme 9 (UBC9); (6358:) ubiquitin-conjugating enzyme E2 [Homo sapiens]; (6359:) Ubiquitin-conjugating enzyme E2 A (Ubiquitin-protein ligase A)(Ubiquitin carrier protein A) (HR6A) (hHR6A); (6360:) Ubiquitin-conjugating enzyme E2 B (Ubiquitin-protein ligase B)(Ubiquitin carrier protein B) (HR6B) (hHR6B) (E2-17 kDa); (6361:) Ubiquitin-conjugating enzyme E2 C (Ubiquitin-protein ligase C)(Ubiquitin carrier protein C) (UbcH10); (6362:) Ubiquitin-conjugating enzyme E2 D1 (Ubiquitin-protein ligase D1)(Ubiquitin carrier protein D1) (UbcH5) (Ubiquitin-conjugatingenzyme E2-17 kDa 1) (E2(17)KB 1); (6363:) Ubiquitin-conjugating enzyme E2 D2 (Ubiquitin-protein ligase D2)(Ubiquitin carrier protein D2) (Ubiquitin-conjugating enzyme E2-17kDa 2) (E2(17)KB 2); (6364:) ubiquitin-conjugating enzyme E2 D2 transcript variant 1 [Homosapiens]; (6365:) Ubiquitin-conjugating enzyme E2 D3 (Ubiquitin-protein ligase D3)(Ubiquitin carrier protein D3) (Ubiquitin-conjugating enzyme E2-17kDa 3) (E2(17)KB 3); (6366:) Ubiquitin-conjugating enzyme E2 E1 (Ubiquitin-protein ligase E1)(Ubiquitin carrier

protein E1) (UbcH6); (6367:) Ubiquitin-conjugating enzyme E2 E2 (Ubiquitin-protein ligase E2)(Ubiquitin carrier protein E2) (UbcH8); (6368:) Ubiquitin-conjugating enzyme E2 E3 (Ubiquitin-protein ligase E3)(Ubiquitin carrier protein E3) (Ubiquitin-conjugating enzyme E2-23kDa) (UbcH9) (UbcM2); (6369:) Ubiquitin-conjugating enzyme E2 G1 (Ubiquitin-protein ligase G1)(Ubiquitin carrier protein G1) (E217K) (UBC7); (6370:) Ubiquitin-conjugating enzyme E2 G2 (Ubiquitin-protein ligase G2)(Ubiquitin carrier protein G2); (6371:) Ubiquitin-conjugating enzyme E2 H (Ubiquitin-protein ligase H)(Ubiquitin carrier protein H) (UbcH2) (E2-20K); (6372:) Ubiquitin-conjugating enzyme E2 J1 (Non-canonicalubiquitin-conjugating enzyme 1) (NCUBE1) (Yeastubiquitin-conjugating enzyme UBC6 homolog E) (HSUBC6e); (6373:) Ubiquitin-conjugating enzyme E2 J2 (Non-canonicalubiquitin-conjugating enzyme 2) (NCUBE2); (6374:) ubiquitin-conjugating enzyme E2 Kua-UEV isoform 1 [Homo sapiens]; (6375:) ubiquitin-conjugating enzyme E2 Kua-UEV isoform 2 [Homo sapiens]; (6376:) Ubiquitin-conjugating enzyme E2 L3 (Ubiquitin-protein ligase L3)(Ubiquitin carrier protein L3) (UbcH7) (E2-F1) (L-UBC); (6377:) Ubiquitin-conjugating enzyme E2 L6 (Ubiquitin-protein ligase L6)(Ubiquitin carrier protein L6) (UbcH8) (Retinoic acid-induced geneB protein) (RIG-B); (6378:) Ubiquitin-conjugating enzyme E2 N (Ubiquitin-protein ligase N)(Ubiquitin carrier protein N) (Ubc13) (Bendless-likeubiquitin-conjugating enzyme); (6379:) Ubiquitin-conjugating enzyme E2 Q1 (Ubiquitin-protein ligase Q1)(Ubiquitin carrier protein Q1) (Protein NICE-5); (6380:) Ubiquitin-conjugating enzyme E2 Q2 (Ubiquitin-protein ligase Q2)(Ubiquitin carrier protein Q2); (6381:) Ubiquitin-conjugating enzyme E2 S (Ubiquitin-protein ligase S)(Ubiquitin carrier protein S) (Ubiquitin-conjugating enzyme E2-24kDa) (E2-EPF5); (6382:) Ubiquitin-conjugating enzyme E2 T (Ubiquitin-protein ligase T)(Ubiquitin carrier protein T); (6383:) Ubiquitin-conjugating enzyme E2 U (Ubiquitin-protein ligase U)(Ubiquitin carrier protein U); (6384:) ubiquitin-conjugating enzyme E2 UbcH-ben [Homo sapiens]; (6385:) Ubiquitin-conjugating enzyme E2 variant 1 (UEV-1) (CROC-1)(Ubiquitin-conjugating enzyme variant Kua) (TRAF6-regulated IKKactivator 1 beta Uev1A); (6386:) Ubiquitin-conjugating enzyme E2 variant 1 [Homo sapiens]; (6387:) ubiquitin-conjugating enzyme E2 variant 1 isoform a [Homo sapiens]; (6388:) ubiquitin-conjugating enzyme E2 variant 1 isoform c [Homo sapiens]; (6389:) ubiquitin-conjugating enzyme E2 variant 1 isoform d [Homo sapiens]; (6390:) Ubiquitin-conjugating enzyme E2 variant 2 (MMS2) (Enterocytedifferentiation-associated factor EDAF-1) (Enterocytedifferentiation-promoting factor) (EDPF-1) (Vitamin D3-inducibleprotein) (DDVit 1); (6391:) ubiquitin-conjugating enzyme E2 variant 2 [Homo sapiens];

(6392:) Ubiquitin-conjugating enzyme E2, J1 (UBC6 homolog, yeast) [Homosapiens]; (6393:) ubiquitin-conjugating enzyme E2, J1 [Homo sapiens]; (6394:) ubiquitin-conjugating enzyme E2, J1 variant [Homo sapiens]; (6395:) Ubiquitin-conjugating enzyme E2, J2 (UBC6 homolog, yeast) [Homosapiens]; (6396:) ubiquitin-conjugating enzyme E2-17kDa [Homo sapiens]; (6397:) Ubiquitin-conjugating enzyme E2-25 kDa (Ubiquitin-protein ligase)(Ubiquitin carrier protein) (E2(25K)) (Huntingtin-interactingprotein 2) (HIP-2); (6398:) Ubiquitin-conjugating enzyme E2-32 kDa complementing(Ubiquitin-protein ligase) (Ubiquitin carrier protein) (E2-CDC34); (6399:) Ubiquitin-conjugating enzyme E2A (RAD6 homolog) [Homo sapiens]; (6400:) ubiquitin-conjugating enzyme E2A isoform 1 [Homo sapiens]; (6401:) ubiquitin-conjugating enzyme E2A isoform 1 variant [Homo sapiens]; (6402:) ubiquitin-conjugating enzyme E2A isoform 2 [Homo sapiens]; (6403:) ubiquitin-conjugating enzyme E2A isoform 3 [Homo sapiens]; (6404:) Ubiquitin-conjugating enzyme E2B (RAD6 homolog) [Homo sapiens]; (6405:) ubiquitin-conjugating enzyme E2B [Homo sapiens]; (6406:) Ubiquitin-conjugating enzyme E2C [Homo sapiens]; (6407:) ubiquitin-conjugating enzyme E2C isoform 1 [Homo sapiens]; (6408:) ubiquitin-conjugating enzyme E2C isoform 2 [Homo sapiens]; (6409:) ubiquitin-conjugating enzyme E2C isoform 3 [Homo sapiens]; (6410:) ubiquitin-conjugating enzyme E2C isoform 4 [Homo sapiens]; (6411:) ubiquitin-conjugating enzyme E2C isoform 5 [Homo sapiens]; (6412:) Ubiquitin-conjugating enzyme E2D 1 (UBC4/5 homolog, yeast) [Homosapiens]; (6413:) ubiquitin-conjugating enzyme E2D 1 [Homo sapiens]; (6414:) Ubiquitin-conjugating enzyme E2D 2 (UBC4/5 homolog, yeast) [Homosapiens]; (6415:) ubiquitin-conjugating enzyme E2D 2 isoform 1 [Homo sapiens]; (6416:) ubiquitin-conjugating enzyme E2D 2 isoform 2 [Homo sapiens]; (6417:) Ubiquitin-conjugating enzyme E2D 3 (UBC4/5 homolog, yeast) [Homosapiens]; (6418:) ubiquitin-conjugating enzyme E2D 3 [Homo sapiens]; (6419:) ubiquitin-conjugating enzyme E2D 3 isoform 1 [Homo sapiens]; (6420:) ubiquitin-conjugating enzyme E2D 3 isoform 2 [Homo sapiens]; (6421:) ubiquitin-conjugating enzyme E2D 3 isoform 3 [Homo sapiens]; (6422:) ubiquitin-conjugating enzyme E2D 4 (putative) [Homo sapiens]; (6423:) Ubiquitin-conjugating enzyme E2E 1 (UBC4/5 homolog, yeast) [Homosapiens]; (6424:) ubiquitin-conjugating enzyme E2E 1 isoform 1 [Homo sapiens]; (6425:) ubiquitin-conjugating enzyme E2E 1 isoform 2 [Homo sapiens]; (6426:) ubiquitin-conjugating enzyme E2E 2 (UBC4/5 homolog, yeast) [Homosapiens]; (6427:) Ubiquitin-conjugating enzyme E2E 3 (UBC4/5 homolog, yeast) [Homosapiens]; (6428:) ubiquitin-conjugating enzyme E2E 3 [Homo sapiens]; (6429:) Ubiquitin-

conjugating enzyme E2F (putative) [Homo sapiens]; (6430:) ubiquitin-conjugating enzyme E2G 1 (UBC7 homolog, C. elegans) [Homosapiens]; (6431:) Ubiquitin-conjugating enzyme E2G 1 (UBC7 homolog, yeast) [Homosapiens]; (6432:) ubiquitin-conjugating enzyme E2G 1 [Homo sapiens]; (6433:) Ubiquitin-conjugating enzyme E2G 2 (UBC7 homolog, yeast) [Homosapiens]; (6434:) ubiquitin-conjugating enzyme E2G 2 isoform 1 [Homo sapiens]; (6435:) ubiquitin-conjugating enzyme E2G 2 isoform 2 [Homo sapiens]; (6436:) ubiquitin-conjugating enzyme E2H (UBC8 homolog, yeast) [Homosapiens]; (6437:) ubiquitin-conjugating enzyme E2H isoform 1 [Homo sapiens]; (6438:) ubiquitin-conjugating enzyme E2H isoform 2 [Homo sapiens]; (6439:) Ubiquitin-conjugating enzyme E2I (UBC9 homolog, yeast) [Homosapiens]; (6440:) ubiquitin-conjugating enzyme E2I [Homo sapiens]; (6441:) ubiquitin-conjugating enzyme E2I variant [Homo sapiens]; (6442:) Ubiquitin-conjugating enzyme E2L 3 [Homo sapiens]; (6443:) ubiquitin-conjugating enzyme E2L 3 isoform 1 [Homo sapiens]; (6444:) ubiquitin-conjugating enzyme E2L 3 isoform 2 [Homo sapiens]; (6445:) Ubiquitin-conjugating enzyme E2L 6 [Homo sapiens]; (6446:) ubiquitin-conjugating enzyme E2L 6 isoform 1 [Homo sapiens]; (6447:) ubiquitin-conjugating enzyme E2L 6 isoform 2 [Homo sapiens]; (6448:) ubiquitin-conjugating enzyme E2-like isoform a [Homo sapiens]; (6449:) ubiquitin-conjugating enzyme E2-like isoform b [Homo sapiens]; (6450:) Ubiquitin-conjugating enzyme E2M (UBC12 homolog, yeast) [Homosapiens]; (6451:) ubiquitin-conjugating enzyme E2M [Homo sapiens]; (6452:) Ubiquitin-conjugating enzyme E2N (UBC13 homolog, yeast) [Homosapiens]; (6453:) ubiquitin-conjugating enzyme E2N [Homo sapiens]; (6454:) ubiquitin-conjugating enzyme E2N-like [Homo sapiens]; (6455:) ubiquitin-conjugating enzyme E2O [Homo sapiens]; (6456:) ubiquitin-conjugating enzyme E2Q (putative) [Homo sapiens]; (6457:) ubiquitin-conjugating enzyme E2Q (putative) 2 [Homo sapiens]; (6458:) ubiquitin-conjugating enzyme E2Q [Homo sapiens]; (6459:) Ubiquitin-conjugating enzyme E2R 2 [Homo sapiens]; (6460:) ubiquitin-conjugating enzyme E2S [Homo sapiens]; (6461:) ubiquitin-conjugating enzyme E2T (putative) [Homo sapiens]; (6462:) ubiquitin-conjugating enzyme E2U (putative) [Homo sapiens]; (6463:) Ubiquitin-conjugating enzyme E2W (putative) [Homo sapiens]; (6464:) ubiquitin-conjugating enzyme E2W (putative) isoform 1 [Homosapiens]; (6465:) ubiquitin-conjugating enzyme E2W (putative) isoform 2 [Homosapiens]; (6466:) ubiquitin-conjugating enzyme E2W (putative) isoform 3 [Homosapiens]; (6467:) ubiquitin-conjugating enzyme E2Z (putative) [Homo sapiens]; (6468:) ubiquitin-conjugating enzyme HBUCE1 [Homo sapiens]; (6469:) ubiquitin-conjugating enzyme isolog [Homo sapiens]; (6470:) ubiquitin-conjugating

enzyme RIG-B [Homo sapiens]; (6471:) ubiquitin-conjugating enzyme UBC3B [Homo sapiens]; (6472:) ubiquitin-conjugating enzyme UbcH2 [Homo sapiens]; (6473:) ubiquitin-conjugating enzyme UbcH6 [Homo sapiens]; (6474:) ubiquitin-conjugating enzyme UbcH7 [Homo sapiens]; (6475:) ubiquitin-conjugating enzyme UbcM2 [Homo sapiens]; (6476:) ubiquitin-conjugating enzyme variant Kua [Homo sapiens]; (6477:) ubiquitin-conjugating enzyme, UBC9 [Homo sapiens]; (6478:) ubiquitin-conjugating enzyme; (6479:) ubiquitin-conjyugating enzyme E2 [Homo sapiens]; (6480:) Ubiquitin-fold modifier conjugating enzyme 1 [Homo sapiens]; (6481:) Ubiquitin-like 1-activating enzyme E1A (SUMO-1-activating enzymesubunit 1); (6482:) Ubiquitin-like 1-activating enzyme E1B (SUMO-1-activating enzymesubunit 2) (Anthracycline-associated resistance ARX); (6483:) Ubiquitin-like PHD and RING finger domain-containing protein 2(Ubiquitin-like-containing PHD and RING finger domains protein 2)(Np95/ICBP90-like RING finger protein) (Np95-like RING fingerprotein) (Nuclear zinc finger protein Np97) (RING finger protein107); (6484:) "ubiquitin-like protein activating enzyme; sentrin activating enzyme[Homo sapiens]."; (6485:) Ubiquitin-protein E3 ligase Topors (SUMO1-protein E3 ligase Topors)(Topoisomerase I-binding RING finger protein) (TopoisomeraseI-binding arginine/serine-rich protein) (Tumor suppressorp53-binding protein 3) (p53-binding protein 3) (p53BP3); (6486:) Ubiquitin-protein ligase BRE1A (BRE1-A) (hBRE1) (RING fingerprotein 20); (6487:) Ubiquitin-protein ligase BRE1B (BRE1-B) (RING finger protein 40)(95 kDa retinoblastoma-associated protein) (RBP95); (6488:) ubiquitin-protein ligase E1 homolog - human; (6489:) Ubiquitin-protein ligase E3A (E6AP ubiquitin-protein ligase)(Oncogenic protein-associated protein E6-AP) (Human papillomavirusE6-associated protein) (NY-REN-54 antigen); (6490:) Ubiquitin-protein ligase E3C; (6491:) Ubiquitin-protein ligase EDD1 (Hyperplastic discs protein homolog)(hHYD) (Progestin-induced protein); (6492:) ubiquitin-specific processing protease [Homo sapiens]; (6493:) ubiquitin-specific protease 12-like 1 [Homo sapiens]; (6494:) ubiquitin-specific protease 21 [Homo sapiens]; (6495:) ubiquitin-specific protease 26 [Homo sapiens]; (6496:) ubiquitin-specific protease 3 [Homo sapiens]; (6497:) ubiquitin-specific protease 31 [Homo sapiens]; (6498:) ubiquitin-specific protease 7 isoform [Homo sapiens]; (6499:) U-box domain containing 5 isoform a [Homo sapiens]; (6500:) U-box domain containing 5 isoform b [Homo sapiens]; (6501:) UDP glucuronosyltransferase (EC 2.4.1.-) 1A10 precursor - human; (6502:) UDP glycosyltransferase 1 family, polypeptide A1 precursor [Homosapiens]; (6503:) UDP glycosyltransferase 1 family, polypeptide A10 precursor [Homosapiens]; (6504:) UDP glycosyltransferase 1 family, polypeptide A3

precursor [Homosapiens]; (6505:) UDP glycosyltransferase 1 family, polypeptide A4 precursor [Homosapiens]; (6506:) UDP glycosyltransferase 1 family, polypeptide A5 precursor [Homosapiens]; (6507:) UDP glycosyltransferase 1 family, polypeptide A6 isoform 1precursor [Homo sapiens]; (6508:) UDP glycosyltransferase 1 family, polypeptide A6 isoform 2 [Homosapiens]; (6509:) UDP glycosyltransferase 1 family, polypeptide A7 precursor [Homosapiens]; (6510:) UDP glycosyltransferase 1 family, polypeptide A8 precursor [Homosapiens]; (6511:) UDP glycosyltransferase 1 family, polypeptide A9 precursor [Homosapiens]; (6512:) UDP glycosyltransferase 2 family, polypeptide B15 [Homo sapiens]; (6513:) UDP glycosyltransferase 2 family, polypeptide B4 [Homo sapiens]; (6514:) UDP glycosyltransferase 8 (UDP-galactose ceramidegalactosyltransferase) [Homo sapiens]; (6515:) UDP-Gal:betaGlcNAc beta 1,3-galactosyltransferase 5 [Homo sapiens]; (6516:) UDP-Gal:betaGlcNAc beta 1,4-galactosyltransferase 1,membrane-bound form [Homo sapiens]; (6517:) UDP-Gal:betaGlcNAc beta 1,4- galactosyltransferase 2 [Homosapiens]; (6518:) UDP-Gal:betaGlcNAc beta 1,4- galactosyltransferase 3 [Homosapiens]; (6519:) UDP-Gal:betaGlcNAc beta 1,4- galactosyltransferase 4 [Homosapiens]; (6520:) UDP-Gal:betaGlcNAc beta 1,4- galactosyltransferase 5 [Homosapiens]; (6521:) UDP-Gal:betaGlcNAc beta 1,4- galactosyltransferase 6 [Homosapiens]; (6522:) UDP-galactose-4-epimerase [Homo sapiens]; (6523:) UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 1 [Homosapiens]; (6524:) UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 2 [Homosapiens]; (6525:) UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 3 [Homosapiens]; (6526:) UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 4 [Homosapiens]; (6527:) UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 5 [Homosapiens]; (6528:) UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 6 [Homosapiens]; (6529:) UDP-glucose 4-epimerase (Galactowaldenase) (UDP-galactose4-epimerase); (6530:) UDP-glucose pyrophosphorylase 2 isoform a [Homo sapiens]; (6531:) UDP-glucose pyrophosphorylase 2 isoform b [Homo sapiens]; (6532:) UDP-glucuronate decarboxylase 1 [Homo sapiens]; (6533:) UDP-glucuronosyltransferase 1-1 precursor(UDP-glucuronosyltransferase 1A1) (UDPGT) (UGT1*1) (UGT1-01)(UGT1.1) (UGT-1A) (UGT1A) (Bilirubin-specific UDPGT isozyme 1)(HUG-BR1); (6534:) UDP-glucuronosyltransferase 1-6 precursor(UDP-glucuronosyltransferase 1A6) (UDPGT) (UGT1*6) (UGT1-06)(UGT1.6) (UGT-1F) (UGT1F) (Phenol-metabolizingUDP-glucuronosyltransferase); (6535:) UDP-glucuronosyltransferase 2B15 precursor (UDPGT) (UDPGTh-3)(HLUG4); (6536:) UDP-

glucuronosyltransferase 2B17 precursor (UDPGT)(C19-steroid-specific UDP-glucuronosyltransferase); (6537:) UDP-glucuronosyltransferase 2B4 precursor (UDPGT) (Hyodeoxycholicacid) (HLUG25) (UDPGTh-1); (6538:) UDP-glucuronyltransferase-S [Homo sapiens]; (6539:) UDP-N-acetylglucosamine-2-epimerase / N-acetylmannosamine kinase[Homo sapiens]; (6540:) UDP-N-acetylglucosamine-2-epimerase [Homo sapiens]; (6541:) UDP-N-acetylglucosamine-2-epimerase/N-acetylmannosamine kinase[Homo sapiens]; (6542:) UDP-N-acetylglucosamine--dolichyl-phosphateN-acetylglucosaminephosphotransferase (GPT) (G1PT)(N-acetylglucosamine-1-phosphate transferase) (GlcNAc-1-Ptransferase); (6543:) UDP-N-acetylglucosamine-dolichyl-phosphateN-acetylglucosaminephosphotransferase isoform a [Homo sapiens]; (6544:) UDP-N-acetylglucosamine-dolichyl-phosphateN-acetylglucosaminephosphotransferase isoform b [Homo sapiens]; (6545:) "UDP-N-acetylhexosamine pyrophosphorylase (Antigen X) (AGX)(Sperm-associated antigen 2) [Includes:) UDP-N-acetylgalactosaminepyrophosphorylase (AGX-1); UDP-N-acetylglucosaminepyrophosphorylase (AGX-2)]."; (6546:) UDP-N-acteylglucosamine pyrophosphorylase 1 [Homo sapiens]; (6547:) UEV-1 [Homo sapiens]; (6548:) UEV1As [Homo sapiens]; (6549:) UEV1Bs [Homo sapiens]; (6550:) Ufm1-conjugating enzyme 1 (Ubiquitin-fold modifier-conjugatingenzyme 1); (6551:) Ufm1-conjugating enzyme 1 [Homo sapiens]; (6552:) UGA suppressor tRNA-associated protein (tRNA(Ser/Sec)-associatedantigenic protein) (SLA/LP autoantigen) (Soluble liver antigen)(SLA) (Liver-pancreas antigen) (LP) (SLA-p35); (6553:) UMP synthase [Homo sapiens]; (6554:) UMP-CMP kinase (Cytidylate kinase) (Deoxycytidylate kinase)(Cytidine monophosphate kinase) (Uridine monophosphate/cytidinemonophosphate kinase) (UMP/CMP kinase) (UMP/CMPK) (Uridinemonophosphate kinase); (6555:) UMP-CMP kinase [Homo sapiens]; (6556:) UnpEL [Homo sapiens]; (6557:) UnpES [Homo sapiens]; (6558:) u-plasminogen activator receptor form 1 precursor - human; (6559:) upstream binding protein 1 (LBP-1a) [Homo sapiens]; (6560:) Upstream-binding protein 1 (LBP-1); (6561:) Uracil-DNA glycosylase (UDG); (6562:) uracil-DNA glycosylase isoform UNG1 precursor [Homo sapiens]; (6563:) uracil-DNA glycosylase isoform UNG2 [Homo sapiens]; (6564:) Urate Transporter 1 (URAT1); (6565:) Urease; (6566:) Uridine diphosphate glucose pyrophosphatase (UDPG pyrophosphatase)(UGPPase) (Nucleoside diphosphate-linked moiety X motif 14) (Nudixmotif 14); (6567:) uridine diphosphate glucose pyrophosphatase [Homo sapiens]; (6568:) uridine phosphorylase (EC 2.4.2.3)-2 - human; (6569:) Uridine Phosphorylase (UrdPase);

(6570:) uridine-cytidine kinase 2 [Homo sapiens]; (6571:) UROD [Homo sapiens]; (6572:) urokinase plasminogen activator preproprotein [Homo sapiens]; (6573:) Urokinase plasminogen activator surface receptor precursor (uPAR)(U-PAR) (Monocyte activation antigen Mo3) (CD87 antigen); (6574:) Urokinase-type plasminogen activator (uPA); (6575:) Urokinase-type plasminogen activator receptor (uPAR); (6576:) Uronyl 2-sulfotransferase; (6577:) uroporphyrinogen decarboxylase (EC 4.1.1.37); (6578:) Uroporphyrinogen decarboxylase (URO-D) (UPD); (6579:) uroporphyrinogen decarboxylase [Homo sapiens]; (6580:) uroporphyrinogen decarboxylase; (6581:) Urotensin II (UT-II) Receptor; (6582:) Urotensin II receptor (UR-II-R) (G-protein coupled receptor 14); (6583:) USP48 protein [Homo sapiens]; (6584:) usurpin beta [Homo sapiens]; (6585:) Usurpin-alpha [Homo sapiens]; (6586:) Usurpin-beta [Homo sapiens]; (6587:) Usurpin-gamma [Homo sapiens]; (6588:) UTP-hexose-1-phosphate uridylyltransferase (EC 2.7.7.10) - human; (6589:) UURF2 ubiquitin ligase [Homo sapiens]; (6590:) Vacuolar ATP synthase 16 kDa proteolipid subunit; (6591:) Vacuolar ATP synthase catalytic subunit A, osteoclast isoform(V-ATPase subunit A 2) (Vacuolar proton pump alpha subunit 2)(V-ATPase 69 kDa subunit 2) (Isoform HO68); (6592:) Vacuolar ATP synthase catalytic subunit A, ubiquitous isoform(V-ATPase subunit A 1) (Vacuolar proton pump alpha subunit 1)(V-ATPase 69 kDa subunit 1) (Isoform VA68); (6593:) Vacuolar ATP synthase subunit B, brain isoform (V-ATPase B2subunit) (Vacuolar proton pump B isoform 2) (Endomembrane protonpump 58 kDa subunit) (HO57); (6594:) Vacuolar ATP synthase subunit B, kidney isoform (V-ATPase B1subunit) (Vacuolar proton pump B isoform 1) (Endomembrane protonpump 58 kDa subunit); (6595:) Vacuolar ATP synthase subunit C (V-ATPase C subunit) (Vacuolarproton pump C subunit); (6596:) Vacuolar ATP synthase subunit D (V-ATPase D subunit) (Vacuolarproton pump D subunit) (V-ATPase 28 kDa accessory protein); (6597:) Vacuolar ATP synthase subunit d (V-ATPase d subunit) (Vacuolarproton pump subunit d) (V-ATPase AC39 subunit) (V-ATPase 40 kDaaccessory protein) (P39) (32 kDa accessory protein); (6598:) Vacuolar ATP synthase subunit E (V-ATPase E subunit) (Vacuolarproton pump E subunit) (V-ATPase 31 kDa subunit) (P31); (6599:) Vacuolar ATP synthase subunit F (V-ATPase F subunit) (Vacuolarproton pump F subunit) (V-ATPase 14 kDa subunit); (6600:) Vacuolar ATP synthase subunit G 1 (V-ATPase G subunit 1) (Vacuolarproton pump G subunit 1) (V-ATPase 13 kDa subunit 1) (Vacuolar ATPsynthase subunit M16); (6601:) Vacuolar ATP synthase subunit G 2 (V-ATPase G subunit 2) (Vacuolarproton pump G subunit 2) (V-ATPase 13 kDa subunit 2); (6602:) Vacuolar ATP synthase subunit G 3 (V-ATPase G subunit 3)

(Vacuolarproton pump G subunit 3) (V-ATPase 13 kDa subunit 3); (6603:) Vacuolar ATP synthase subunit H (V-ATPase H subunit) (Vacuolarproton pump subunit H) (V-ATPase 50/57 kDa subunits) (Vacuolarproton pump subunit SFD) (VMA13) (Nef-binding protein 1) (NBP1); (6604:) vacuolar ATPase subunit H [Homo sapiens]; (6605:) vacuolar H+ ATPase C2 isoform a [Homo sapiens]; (6606:) vacuolar H+ ATPase C2 isoform b [Homo sapiens]; (6607:) vacuolar H+ ATPase E1 isoform a [Homo sapiens]; (6608:) vacuolar H+ ATPase E1 isoform b [Homo sapiens]; (6609:) vacuolar H+ ATPase E1 isoform c [Homo sapiens]; (6610:) vacuolar H+ ATPase G1 [Homo sapiens]; (6611:) vacuolar H+ATPase B2 [Homo sapiens]; (6612:) Vacuolar Hydrogen Transporting ATPase (V-ATPase); (6613:) Vacuolar protein sorting-associated protein 26A (Vesicle proteinsorting 26A) (hVPS26); (6614:) Vacuolar protein sorting-associated protein 26B (Vesicle proteinsorting 26B); (6615:) Vacuolar protein sorting-associated protein 29 (Vesicle proteinsorting 29) (hVPS29) (PEP11); (6616:) Vacuolar protein sorting-associated protein 35 (Vesicle proteinsorting 35) (hVPS35) (Maternal-embryonic 3); (6617:) vacuolar proton pump subunit SFD alpha isoform [Homo sapiens]; (6618:) Vacuolar proton translocating ATPase 116 kDa subunit a isoform 1(V-ATPase 116 kDa isoform a1) (Clathrin-coated vesicle/synapticvesicle proton pump 116 kDa subunit) (Vacuolar proton pump subunit1) (Vacuolar adenosine triphosphatase subunit Ac116); (6619:) Vacuolar proton translocating ATPase 116 kDa subunit a isoform 2(V-ATPase 116 kDa isoform a2) (TJ6); (6620:) Vacuolar proton translocating ATPase 116 kDa subunit a isoform 3(V-ATPase 116 kDa isoform a3) (Osteoclastic proton pump 116 kDasubunit) (OC-116 kDa) (OC116) (T-cell immune regulator 1) (T cellimmune response cDNA7 protein) (TIRC7); (6621:) Vacuolar proton translocating ATPase 116 kDa subunit a isoform 4(V-ATPase 116 kDa isoform a4) (Vacuolar proton translocating ATPase116 kDa subunit a kidney isoform); (6622:) v-akt murine thymoma viral oncogene homolog 1 [Homo sapiens]; (6623:) v-akt murine thymoma viral oncogene homolog 2 [Homo sapiens]; (6624:) Valacyclovir hydrolase precursor (VACVase) (Biphenyl hydrolase-likeprotein) (Biphenyl hydrolase-related protein) (Bph-rp) (Breastepithelial mucin-associated antigen) (MCNAA); (6625:) valosin containing protein (p97)/p47 complex interacting protein 1[Homo sapiens]; (6626:) Valyl-tRNA synthetase (Valine--tRNA ligase) (ValRS) (Protein G7a); (6627:) Vanilloid Receptor 1 (VR1); (6628:) Vascular Adhesion Protein-1 (VAP-1) Receptor; (6629:) vascular adhesion protein-1 [Homo sapiens]; (6630:) Vascular Adhesion Protein-1/Semicarbazide-Sensitive Amine Oxidase (VAP-1/SSAO); (6631:) "vascular adhesion protein-1; semicarbazide sensitive amine oxidase;copper-

containing amine oxidase homolog [Homo sapiens]."; (6632:) Vascular Cell Adhesion Molecule-1 (VCAM-1) Expression; (6633:) Vascular Endothelial Growth Factor (VEGF); (6634:) Vascular Endothelial Growth Factor (VEGF) Receptor; (6635:) Vascular Endothelial Growth Factor 121 (VEGF121); (6636:) Vascular Endothelial Growth Factor 145 (VEGF145); (6637:) Vascular Endothelial Growth Factor 165 (VEGF165); (6638:) Vascular Endothelial Growth Factor 165 (VEGF165) Receptor; (6639:) vascular endothelial growth factor A isoform a precursor [Homosapiens]; (6640:) vascular endothelial growth factor A isoform b precursor [Homosapiens]; (6641:) vascular endothelial growth factor A isoform c precursor [Homosapiens]; (6642:) vascular endothelial growth factor A isoform d precursor [Homosapiens]; (6643:) vascular endothelial growth factor A isoform e precursor [Homosapiens]; (6644:) vascular endothelial growth factor A isoform f precursor [Homosapiens]; (6645:) vascular endothelial growth factor A isoform g precursor [Homosapiens]; (6646:) Vascular Endothelial Growth Factor Receptor 1 (VEGFR-1); (6647:) Vascular endothelial growth factor receptor 1 precursor (VEGFR-1)(Vascular permeability factor receptor) (Tyrosine-protein kinasereceptor FLT) (Flt-1) (Tyrosine-protein kinase FRT) (Fms-liketyrosine kinase 1); (6648:) Vascular Endothelial Growth Factor Receptor 2 (VEGFR-2); (6649:) Vascular endothelial growth factor receptor 2 precursor (VEGFR-2)(Kinase insert domain receptor) (Protein-tyrosine kinase receptorFlk-1) (CD309 antigen); (6650:) Vascular endothelial growth factor receptor 3 precursor (VEGFR-3)(Tyrosine-protein kinase receptor FLT4); (6651:) Vascular Endothelial Growth Factor Receptor1-Tyrosine Kinase (VEGFR1-TK); (6652:) Vascular Endothelial Growth Factor Receptor2-Tyrosine Kinase (VEGFR2-TK); (6653:) Vascular Endothelial Growth Factor Receptor-Tyrosine Kinase (VEGFR-TK); (6654:) Vascular Endothelial-Cadherin (VE-Cadherin); (6655:) Vasoactive Intestinal Peptide Receptor 1 (VPAC1); (6656:) vasoactive intestinal peptide receptor-related protein precursor(clone hIVR5) - human; (6657:) Vasoactive intestinal polypeptide receptor 1 precursor (VIP-R-1)(Pituitary adenylate cyclase-activating polypeptide type IIreceptor) (PACAP type II receptor) (PACAP-R-2); (6658:) Vasoactive intestinal polypeptide receptor 2 precursor (VIP-R-2)(Pituitary adenylate cyclase-activating polypeptide type IIIreceptor) (PACAP type III receptor) (PACAP-R-3)(Helodermin-preferring VIP receptor); (6659:) Vasopressin V1a receptor (V1aR) (Vascular/hepatic-type argininevasopressin receptor) (Antidiuretic hormone receptor 1a) (AVPRV1a); (6660:) Vasopressin V1b receptor (V1bR) (AVPR V1b) (Vasopressin V3receptor) (AVPR V3) (Antidiuretic hormone receptor 1b); (6661:) Vasopressin V2 receptor (Renal-type arginine vasopressin

receptor)(Antidiuretic hormone receptor) (AVPR V2); (6662:) VELF1904 [Homo sapiens]; (6663:) Very low-density lipoprotein receptor precursor (VLDL receptor)(VLDL-R); (6664:) Very-long-chain acyl-CoA synthetase (VLCS)(Very-long-chain-fatty-acid-CoA ligase) (VLACS) (THCA-CoA ligase)(Fatty-acid-coenzyme A ligase, very long-chain 1)(Long-chain-fatty-acid--CoA ligase) (Fatty acid transport protein2) (FATP-2) (Solute carrier family 27 member 2); (6665:) vesicle docking protein p115 [Homo sapiens]; (6666:) Vesicle-associated membrane protein 8 (VAMP-8) (Endobrevin) (EDB); (6667:) v-ets erythroblastosis virus E26 oncogene homolog 1 [Homo sapiens]; (6668:) visfatin precursor [Homo sapiens]; (6669:) Visual pigment-like receptor peropsin; (6670:) vitamin D (1,25-dihydroxyvitamin D3) receptor [Homo sapiens]; (6671:) vitamin D inducible protein [Homo sapiens]; (6672:) Vitamin D Receptor (VDR); (6673:) Vitamin D3 receptor (VDR) (1,25-dihydroxyvitamin D3 receptor); (6674:) Vitamin K; (6675:) Vitamin K epoxide reductase complex subunit 1 (Vitamin K12,3-epoxide reductase subunit 1); (6676:) vitamin K epoxide reductase complex, subunit 1 isoform 1 [Homosapiens]; (6677:) vitamin K epoxide reductase complex, subunit 1 isoform 2 [Homosapiens]; (6678:) "Vitamin K-dependent protein C precursor (Autoprothrombin IIA)(Anticoagulant protein C) (Blood coagulation factor XIV) [Contains:Vitamin K-dependent protein C light chain; Vitamin K-dependentprotein C heavy chain; Activation peptide]."; (6679:) Vitamin K-dependent protein Z precursor; (6680:) v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homologprecursor [Homo sapiens]; (6681:) v-maf musculoaponeurotic fibrosarcoma oncogene homolog G [Homosapiens]; (6682:) v-maf musculoaponeurotic fibrosarcoma oncogene homolog isoform a[Homo sapiens]; (6683:) v-maf musculoaponeurotic fibrosarcoma oncogene homolog isoform b[Homo sapiens]; (6684:) Vomeronasal type-1 receptor 1 (V1r-like receptor 1) (Vomeronasalolfactory receptor chromosome 19 subtype I member 1) (V3r-relatedgene) (hGPCR24); (6685:) Vomeronasal type-1 receptor 2 (V1r-like receptor 2) (hGPCR25); (6686:) Vomeronasal type-1 receptor 3 (V1r-like receptor 3); (6687:) Vomeronasal type-1 receptor 4 (V1r-like receptor 4) (hGPCR27); (6688:) Vomeronasal type-1 receptor 5 (V1r-like receptor 5) (hGPCR26); (6689:) Von Hippel-Lindau disease tumor suppressor (pVHL) (G7 protein); (6690:) von Hippel-Lindau tumor suppressor isoform 1 [Homo sapiens]; (6691:) von Hippel-Lindau tumor suppressor isoform 2 [Homo sapiens]; (6692:) von Willebrand Factor (vWF) Receptor; (6693:) von Willebrand factor preproprotein [Homo sapiens]; (6694:) v-raf murine sarcoma 3611 viral oncogene homolog [Homo sapiens]; (6695:) v-raf murine sarcoma viral oncogene homolog B1 [Homo sapiens]; (6696:) v-raf-1 murine

leukemia viral oncogene homolog 1 [Homo sapiens]; (6697:) v-rel reticuloendotheliosis viral oncogene homolog A, nuclearfactor of kappa light polypeptide gene enhancer in B-cells 3, p65[Homo sapiens]; (6698:) wax synthase [Homo sapiens]; (6699:) Wee1-like protein kinase (Wee1A kinase) (WEE1hu); (6700:) Werner syndrome protein [Homo sapiens]; (6701:) Wiskott-Aldrich syndrome protein [Homo sapiens]; (6702:) Wnt; (6703:) WW, C2 and coiled-coil domain containing 1 [Homo sapiens]; (6704:) xanthine dehydrogenase [Homo sapiens]; (6705:) "Xanthine dehydrogenase/oxidase [Includes:) Xanthine dehydrogenase(XD); Xanthine oxidase (XO) (Xanthine oxidoreductase)]."; (6706:) Xanthine Oxidase (XO); (6707:) X-Linked inhibitor of Apoptosis Protein (XIAP); (6708:) X-linked interleukin-1 receptor accessory protein-like 1 precursor(IL1RAPL-1) (Oligophrenin-4) (Three immunoglobulindomain-containing IL-1 receptor-related 2) (TIGIRR-2); (6709:) X-linked interleukin-1 receptor accessory protein-like 2 precursor(IL1RAPL-2-related protein) (Interleukin-1 receptor 9) (IL-1R9)(IL-1 receptor accessory protein-like 2) (Three immunoglobulindomain-containing IL-1 receptor-related 1) (TIGIRR-1); (6710:) X-linked phosphate regulating endopeptidase homolog [Homo sapiens]; (6711:) X-prolyl aminopeptidase (aminopeptidase P) 1, soluble [Homosapiens]; (6712:) X-prolyl aminopeptidase 2, membrane-bound [Homo sapiens]; (6713:) xylosylprotein beta 1,4-galactosyltransferase 7 [Homo sapiens]; (6714:) Xylosyltransferase 1 (Xylosyltransferase I) (XylT-I) (XT-I)(Peptide O-xylosyltransferase 1); (6715:) Xylosyltransferase 2 (Xylosyltransferase II) (xylT-II) (XT-II)(Peptide O-xylosyltransferase 1); (6716:) xylosyltransferase I [Homo sapiens]; (6717:) xylosyltransferase II [Homo sapiens]; (6718:) Xaa-Pro aminopeptidase 1 (X-Pro aminopeptidase 1) (X-prolylaminopeptidase 1, soluble) (Cytosolic aminopeptidase P) (Solubleaminopeptidase P) (sAmp) (Aminoacylproline aminopeptidase); (6719:) Xaa-Pro dipeptidase (X-Pro dipeptidase) (Proline dipeptidase)(Prolidase) (Imidodipeptidase); (6720:) Xaa-Pro dipeptidase [Homo sapiens]; (6721:) Yama protein; (6722:) Ymer protein long isoform [Homo sapiens]; (6723:) Ymer protein short isoform [Homo sapiens]; (6724:) YOD1 OTU deubiquinating enzyme 1 homolog [Homo sapiens]; (6725:) Zinc finger FYVE domain-containing protein 9 (Mothers againstdecapentaplegic homolog-interacting protein) (Madh-interactingprotein) (Smad anchor for receptor activation) (Receptor activationanchor) (hSARA) (Novel serine protease) (NSP); (6726:) zinc finger protein 146 [Homo sapiens]; (6727:) zinc finger protein Cezanne [Homo sapiens]; (6728:) Zinc finger protein OZF (Only zinc finger protein) (Zinc fingerprotein 146); (6729:) zinc metalloproteinase STE24 homolog [Homo sapiens]; (6730:) Zinc

phosphodiesterase ELAC protein 1 (Ribonuclease Z 1) (RNase Z1) (tRNase Z 1) (tRNA 3 endonuclease 1) (ElaC homolog protein 1)(Deleted in Ma29); (6731:) Zinc phosphodiesterase ELAC protein 2 (Ribonuclease Z 2) (RNase Z2) (tRNase Z 2) (tRNA 3 endonuclease 2) (ElaC homolog protein 2)(Heredity prostate cancer protein 2); (6732:) Zona pellucida sperm-binding protein 2 precursor (Zona pellucidaglycoprotein ZP2) (Zona pellucida protein A)

Methods for isolating “lead compounds”

The present invention in one embodiment is also directed to a method for isolating novel “drug leads” or “lead compounds” from libraries of different molecules synthesised by the methods of the invention. A “drug lead” or “lead compound” is a compound which may not in itself be suitable as a drug, but which exhibits a number of characteristics which are interesting when viewed from the point of view of medical therapy.

The reasons why such “lead compounds” are often unsuitable could be toxicity, unsuitable pharmacokinetic or pharmacodynamic properties, difficulties relating to preparation and purification etc. In such cases, the “lead compound” is used as a model for de novo synthesis of other chemical compounds which are designed so as to be related to the active part of the lead compound in 3D structure and distribution of charged, polar and non-polar groups.

This approach can be refined by initially identifying the members of the library by methods of structure-based or nonstructure based computer drug-modelling. Suitable non-structure based methods are disclosed in e.g. US 5,307,287 and US 5,025,388 (a method known as CoMFA). An alternative is HASL (Hypothetical Active Site Lattice ; Hypothesis Software). Both these methods are based on 3D-QSAR. A feasible structure-based approach is e. g. disclosed in WO 95/06293.

In view of the above, the present invention also pertains to a method for the preparation of a medicinal product, the method comprising the steps of

a) selecting a chemical compound by the methods of the invention described above,
b) performing pre-clinical tests with the chemical compound in order to assess the suitability thereof as a medicinal product,

c) entering, if the chemical compound is deemed suitable in step (b), clinical trials using the chemical compound in order to obtain market authorization for a medicinal product including the chemical compound as a pharmaceutically active substance, and
d) upon grant of a market authorization, admixing the chemical compound with a pharmaceutically acceptable carrier excipient or diluent and marketing the thus obtained medicinal product.

The above-outlined methods should take into consideration all necessary requirements in order to meet GCP and GMP standards.

Additional preferred uses and embodiments of the present invention is disclosed herein below. A number of assays which can be used to verify or identify an effect or popperty of a molecule identified by one or more methods of the present invention can be performed by a person skilled in the art.

In embodiments of the present invention, the bioactive species encoding it is used to identify pharmaceutically relevant target molecules, i.e. the molecules with which the bioactive species can form an interaction. As will be appreciated by those in the art, there can be primary target molecules to which the bioactive species binds or acts upon directly and there can be secondary target molecules, which are part of a signalling pathway affected by the bioactive species; the latter might be termed "validated targets".

In one embodiment, the present methods are useful in cancer applications. The ability to rapidly and specifically kill tumor cells is a cornerstone of cancer chemotherapy. In general, using the methods of the present invention, bioactive species can be identified which, when introduced into any tumor cell (primary or cultured), induce apoptosis, cell death loss of cell division or decreased cell growth. This can be done de novo, or by biased randomization toward known cancer agents, such as angiostatin, which inhibits blood vessel wall growth. According to one embodiment of the present invention, the methods for synthesising a molecule linked to a single stranded identifier oligonucleotide is targeted to a target compound known to be involved in induction of apoptosis, cell death loss of cell division or decreased cell growth.

Targets can include e.g. known proteins such as Abl, Src, Ras, and others, which lead to abnormal cell growth in certain cells or the development of micro-metastases. Thus, in one embodiment, bioactive species obtainable by the methods of the invention are introduced into cancer cells to select for bioactive species which reverse or correct a cancer condition. One of the signal features of oncogene activity in cells is the loss of contact inhibition and the ability to grow in soft-agar. When e.g. Abl, Src, or Ras are expressed 3T3 cells and subjected to puromycin selection, all of the 3T3 cells hyper-transform and detach from the plate. The cells can be removed by washing with fresh medium. This can serve as the basis of a screen, since cells which express a bioactive species having anti-cancer activity will remain attached to the plate and form colonies.

Similarly, the growth and/or spread of certain tumor types is enhanced by stimulatory responses from growth factors and cytokines (PDGF, EGF, Heregulin, and others) which bind to receptors on the surfaces of specific tumors. In one embodiment, the bioactive species obtainable by the methods of the invention are used to inhibit or stop tumor growth and/or spread selecting bioactive species capable of blocking the ability of the growth factor or cytokine to stimulate the tumor cell. The introduction of bioactive species obtainable by the methods of the present invention into specific tumor cells with the addition of the growth factor or cytokine, followed by selection of bioactive species which block the binding, signaling, phenotypic and/or functional responses of these tumor cells to the growth factor or cytokine in question, represent one embodiment of the present invention.

Similarly, the spread of cancer cells (invasion and metastasis) is a significant problem limiting the success of cancer therapies. The ability to inhibit the invasion and/or migration of specific tumor cells would be a significant advance in the therapy of cancer. Tumor cells known to have a high metastatic potential (for example, melanoma, lung cell carcinoma, breast and ovarian carcinoma) can have bioactive species obtainable by the methods of the present invention introduced into them, and bioactive species selected which in a migration or invasion assay, inhibit the migration and/or invasion of specific tumor cells. Particular applications for inhibition of the metastatic phenotype, which could allow a more specific inhibition of metastasis, include the polypeptide encoded by the metastasis suppressor gene NM23, which codes for a dinucleoside diphosphate kinase. Thus, bioactive species acting as activators of this gene could block metastasis. Many oncogene products

also enhance metastasis.

Bioactive species which inactivate or counteract gene products encoded by mutated RAS oncogenes, v-MOS, v-RAF, A-RAF, v-SRC, v-FES, and v-FMS would also act as anti-metastatics. Bioactive species obtainable by the invention which act intracellularly to block the release of combinations of proteases required for invasion, such as the matrix metalloproteases and urokinase, could also be effective antimetastatics.

In one embodiment, the bioactive species obtainable by the methods of the present invention are introduced into tumor cells known to have inactivated tumor suppressors, and successful reversal e.g. by compensation of suppression of the suppressor can be screened for e.g. by restoration of a normal phenotype. A major example is the reversal of p53-inactivating mutations, which are present in 50% or more of all cancers. Since p53's actions are complex and involve its action as a transcription factor, there are probably numerous potential ways a small molecule bioactive species could reverse the mutation. One example could be e.g. to increase the activity of the cyclin-dependent kinase p21CIP1NVAF1. To be useful such reversal would have to work for many of the different known p53 mutations. It is possible to screen for one or more small molecules possessing the above-cited activities.

In another embodiment, the methods of the present invention for synthesising and selecting small molecule bioactive species are useful in various cardiovascular applications. In one embodiment, cardiomyocytes can be screened for the prevention of cell damage or death in the presence of normally injurious conditions, including, but not limited to, the presence of toxic drugs (particularly chemotherapeutic drugs), for example, to prevent heart failure following treatment with adriamycin; anoxia, for example in the setting of coronary artery occlusion; and autoimmune cellular damage by attack from activated lymphoid cells (for example as seen in post viral myocarditis and lupus). Candidate bioactive species are inserted into cardiomyocytes, the cells are subjected to the insult. It is possible to screen for bioactive species are selected that prevent any or all of: apoptosis; membrane depolarization (i.e. decrease arrythmogenic potential of insult); cell swelling; or leakage of specific intracellular ions, second messengers and activating molecules (for example, arachidonic acid andlor lysophosphatidic acid).

In yet another embodiment, the bioactive species obtainable by the methods of the present invention are used to screen for diminished arrhythmia potential in cardiomyocytes. The screens comprise the introduction of the candidate bioactive species, followed by the application of arrythmogenic insults, with screening for bioactive species that block specific depolarization of cell membrane. This can be detected using patch clamps, or via fluorescence techniques). Similarly, channel activity (for example, potassium and chloride channels) in cardiomyocytes could be regulated using the bioactive species obtainable by the methods of the present invention in order to enhance contractility and prevent or diminish arrhythmias.

In yet another embodiment, the bioactive species obtainable by the methods of the present invention are used to screen for enhanced contractile properties of cardiomyocytes and diminish heart failure potential. The introduction of the bioactive species obtainable by the methods of the present invention followed by measuring the rate of change of myosin polymerization/depolymerization using fluorescent techniques can be done. It is possible to screen for bioactive species which increase the rate of change of this phenomenon can result in a greater contractiie response of the entire myocardium, similar to the effect seen with digitalis.

In a still further embodiment, selected bioactive species obtainable by the methods of the present invention can be useful for identifying agents involved in the regulation of intracellular and sarcolemmal calcium cycling in cardiomyocytes in order to prevent arrhythmias. It is possible to screen for bioactive species which regulate sodium-calcium exchange, sodium proton pump function, and regulation of calcium-ATPase activity in human or animal cells.

In one embodiment, the bioactive species obtainable by the methods of the present invention are useful for identifying agents that diminish embolic phenomena in arteries and arterioles leading to strokes (and other occlusive events leading to kidney failure and limb ischemia) and angina precipitating a myocardial infarct are selected. For example, it is possible to screen for bioactive species which will diminish the adhesion of platelets and leukocytes, and thus diminish the occlusion events.

Adhesion in this setting can be inhibited by the bioactive species obtainable by the

methods of the present invention once such bioactive species are inserted into endothelial cells (quiescent cells, or activated by cytokines, i.e. IL-l, and growth factors, i.e. PDGF I EGF) and then screened for either: 1) downregulation of adhesion molecule expression on the surface of the endothelial cells (binding assay); 2) blocking of adhesion molecule activation on the surface of these cells (signaling assay); or 3) releasing in an autocrine manner biological molecules including pepetides that block receptor binding to the cognate receptor on the adhering cell.

Embolic phenomena can also be addressed by activating proteolytic enzymes on the cell surfaces of endothelial cells, and thus releasing active enzyme which can digest blood clots. Thus, the bioactive species obtainable by the methods of the present invention can be introduced into endothelial cells, followed by standard fluorogenic assays, which will allow monitoring of proteolytic activity on the cell surface towards a known substrate. Bioactive species can then be selected which activate specific enzymes towards specific substrates.

In one embodiment, arterial inflammation in the setting of vasculitis and post-infarction can be regulated by decreasing the chemotactic responses of leukocytes and mononuclear leukocytes. This can be accomplished by blocking chemotactic receptors and their responding pathways on these cells. Candidate bioactive species can thus be inserted into these cells, and one can screen for inhibition of the chemotactic response to diverse chemokines (for example, to the IL-8 family of chemokines, RANTES) in cell migration assays.

In yet another embodiment, arterial restenosis following coronary angioplasty can be controlled by regulating the proliferation of vascular intimal cells and capillary and/or arterial endothelial cells. Candidate bioactive species can be inserted into these cell types and their proliferation in response to specific stimuli can be monitored. It is possible to screen for bioactive species which are capable of blocking the expression or function of c-myc and other oncogene products in smooth muscle cells to stop their proliferation. It would also be possible to introduce the bioactive species obtainable by the methods of the present invention into vascular smooth muscle cells and to screen for bioactive species which can selectively induce apoptosis.

Application of small molecule bioactive species may require targeted drug delivery; this is available e.g. with stents, hydrogel coatings, and infusion-based catheter systems. Bioactive species which down regulate endothelin-1A receptors or which block the release of the potent vasoconstrictor and vascular smooth muscle cell mitogen endothelin-l may also be candidates for therapeutics. Accordingly, it is psossible to screen for bioactive species which can inhibit growth of these cells, or which prevent the adhesion of other cells in the circulation known to release autocrine growth factors, such as platelets (PDGF) and mononuclear leukocytes.

The control of capillary and blood vessel growth is an important goal in order to promote increased blood flow to ischemic areas (growth), or to cut-off the blood supply (angiogenesis inhibition) of tumors. Candidate bioactive species can be inserted into capillary endothelial cells and the growth of such cells can be monitored. Stimuli such as low oxygen tension and varying degrees of angiogenic factors can regulate the responses, and one can screen for bioactive species which can produce the appropriate phenotype. Screening for bioactive species capable of acting as antagonisms of vascular endothelial cell growth factor, important in angiogenesis, would also be useful.

In one embodiment, the bioactive species obtainable by the methods of the present invention are useful in screening for decreases in atherosclerosis producing mechanisms to find biological molecules that regulate LDL and HDL metabolism. Candidate bioactive species can be inserted into the appropriate cells (including hepatocytes, mononuclear leukocytes, endothelial cells) and one can screen for bioactive species which lead to a decreased release of LDL or diminished synthesis of LDL, or conversely to an increased release of HDL or enhanced synthesis of HDL. It is also possible to screen for bioactive species which decreases the production of oxidized LDL, which has been implicated in atherosclerosis and isolated from atherosclerotic lesions. This could occur e.g. by activating reducing systems or enzymes, or blocking the activity or production of enzymes implicated in production of oxidized LDL, such as 1 5-lipoxygenase in macrophages.

In one embodiment, the bioactive species obtainable by the methods of the present invention are used in screens to regulate obesity via the control of food intake mechanisms or diminishing the responses of receptor signaling pathways that regulate metabolism. One can screen for bioactive species that regulate or inhibit

the responses of neuropeptide Y (NPY), cholecystokinin and galanin receptors. Candidate bioactive species can be inserted into cells that have these receptors cloned into them, and one can screen for bioactive species which block the signaling responses to galanin and NPY. In a similar manner, one can screen for bioactive species which regulate the leptin receptor.

In a still further embodiment, bioactive species obtainable by the methods of the present invention can be used in screens in neurobiology applications. Candidate bioactive species can be used for screening for anti-apoptotics for preservation of neuronal function and prevention of neuronal death. Initial screens would be done in cell culture. One application would include prevention of neuronal death, by apoptosis, in cerebral ischemia resulting from stroke. Apoptosis is known to be blocked by neuronal apoptosis inhibitory polypeptide (NAIP); screens for its upregulation, or effecting any coupled step could yield bioactive species which selectively block neuronal apoptosis. Other applications include neurodegenerative diseases such as Alzheimer's disease and Huntington's disease.

In another embodiment, bioactive species obtainable by the methods of the present invention can be used in screens in bone biology applications. Osteoclasts are known to play a key role in bone remodeling by breaking down "old" bone, so that osteoblasts can lay down "new" bone. In osteoporosis one has an imbalance of this process. A screen for osteoclast overactivity can be set up by introducing candidate bioactive species to these cells, and then screening for bioactive species that produce: 1) a diminished processing of collagen by these cells; 2) decreased pit formation on bone chips; and 3) decreased release of calcium from bone fragments.

The bioactive species obtainable by the methods of the present invention can also be used in screens for agonists of bone morphogenic biological molecules and hormone mimetics to stimulate, regulate, or enhance new bone formation (in a manner similar to parathyroid hormone and calcitonin, for example). These have use in osteoporosis, for poorly healing fractures, and to accelerate the rate of healing of new fractures. Furthermore, cell lines of connective tissue origin can be treated with candidate bioactive species and screened for their growth, proliferation, collagen stimulating activity, and/or proline incorporating ability on the target osteoblasts. Alternatively, candidate bioactive species can be screened for their ability to increase production of collagen or bone.

In one embodiment, bioactive species obtainable by the methods of the present invention can be screened for activities which are useful in various skin biology applications. Keratinocyte responses to a variety of stimuli may result in psoriasis, a proliferative change in these cells. Candidate bioactive species can be inserted into cells removed from active psoriatic plaques, and one can screen for bioactive species which decrease the rate of growth of these cells.

In one embodiment, the bioactive species obtainable by the methods of the present invention can be screened for activities which are useful in the regulation or inhibition of keloid formation (i.e. excessive scarring). Candidate bioactive species can be introduced into skin connective tissue cells isolated from individuals with this condition, and one can screen for bioactive species that decrease proliferation, collagen formation, or proline incorporation. Results from this work can be extended to treat the excessive scarring that also occurs in burn patients. If a common bioactive species motif is found in the context of the keloid work, then it can be tested if this motif can be used widely in a topical manner to diminish scarring post burn.

Similarly, wound healing for diabetic ulcers and other chronic "failure to heal" conditions in the skin and extremities can be regulated by providing additional growth signals to cells which populate the skin and dermal layers. Growth factor mimetics may in fact be very useful for this condition. Candidate bioactive species can be inserted into skin connective tissue cells, and one can screen for bioactive species which promote the growth of these cells under "harsh" conditions, such as low oxygen tension, low pH, and the presence of inflammatory mediators.

Cosmeceutical applications of the present invention include the control of melanin production in skin melanocytes. A naturally occurring peptide, arbutin, is a tyrosine hydroxylase inhibitor, a key enzyme in the synthesis of melanin. Candidate bioactive species can be introduced into melanocytes and known stimuli that increase the synthesis of melanin applied to the cells. One can screen for bioactive species which inhibit the synthesis of melanin under these conditions.

In one embodiment, one can screen for activities of bioactive species obtainable by the methods of the present invention which are useful in endocrinology applications.

The methods of the present invention and the bioactive species thus obtained can be applied broadly to any endocrine, growth factor, cytokine or chemokine network which involves a signaling peptide or polypeptide that acts in either an endocrine, paracrine or autocrine manner that binds or dimerizes a receptor and activates a signaling cascade that results in a known phenotypic or functional outcome. One can screen for bioactive species which either mimics a desired hormone (i.e., insulin, leptin, calcitonin, PDGF, EGF, EPO, GMCSF, IL1-17, mimetics) or inhibits its action by either blocking the release of the hormone, blocking its binding to a specific receptor or carrier polypeptide (for example, CRF binding polypeptide), or inhibiting the intracellular responses of the specific target cells to that hormone. It is also possible to screen for bioactive species which increase the expression or release of hormones from cells which normally produce them. This would have broad applications in conditions of hormonal deficiency.

In one embodiment, one can screen for activities of bioactive species obtainable by the methods of the present invention which are useful in infectious disease applications. Viral latency (herpes viruses such as CMV, EBV, HBV, and other viruses such as HIV) and their reactivation are a significant problem, particularly in immunosuppressed patients (patients with AIDS and transplant patients). The ability to block the reactivation and spread of these viruses is an important goal. Cell lines known to harbor or be susceptible to latent viral infection can be infected with the specific virus, and then stimuli applied to these cells which have been shown to lead to reactivation and viral replication. This can be followed by measuring viral titers in the medium and scoring cells for phenotypic changes. Candidate bioactive species can then be introduced into these cells under the above conditions, and one can screen for bioactive species which block or diminish the growth and/or release of the virus. As with chemotherapeutics, these experiments can also be done in combination with drugs which are only partially effective towards this outcome, and one can screen for bioactive species which enhance the virucidal effect of these drugs.

One example of many is the ability to block HIV-1 infection. HIV-1 requires CD4 and a co-receptor which can be one of several seven transmembrane G-polypeptide coupled receptors. In the case of the infection of macrophages, CCR-5 is the required coreceptor, and there is strong evidence that a block on CCR-5 will result in resistance to HIV-1 infection. There are two lines of evidence for this statement.

First, it is known that the natural ligands for CCR-5, the CC chemokines RANTES, MIPla and MIPlb are responsible for CD8+ mediated resistance to HIV. Second, individuals homozygous for a mutant allele of CCR-5 are completely resistant to HIV infection. Accordingly, one can screen for activities of bioactive species obtainable by the methods of the present invention which are inhibitory for CCR-5/HIV interaction.

Viruses are known to enter cells using specific receptors to bind to cells (for example, HIV uses CD4, coronavirus uses CD13, murine leukemia virus uses transport polypeptide, and measles virus usesCD44) and to fuse with cells (HIV uses chemokine receptor). Candidate bioactive species can be introduced into target cells known to be permissive to these viruses, and one can screen for bioactive species which block the ability of these viruses to bind to and fuse with specific target cells.

In one embodiment, one can screen for activities of bioactive species obtainable by the methods of the present invention which have applications in the area of infectious organisms. Intracellular organisms such as mycobacteria, listeria, salmonella, pneumocystis, yersinia, leishmania, T. cruzi, can persist and replicate within cells, and become active in immunosuppressed patients. There are currently drugs on the market and in development which are either only partially effective or ineffective against these organisms. Candidate bioactive species can be inserted into specific cells infected with these organisms (pre- or post-infection), and one can screen for bioactive species which promote the intracellular destruction of these organisms in a manner analogous to intracellular "antibiotic bioactive species" similar to magainins. In addition, one can screen for bioactive species which enhance the cidal properties of drugs already under investigation which have insufficient potency by themselves, but, when combined with one or more bioactive species obtainable by the methods of the present invention, are dramatically more potent through a synergistic mechanism or otherwise. One can screen for bioactive species which alter the metabolism of these intracellular organisms, in such a way as to terminate their intracellular life cycle by inhibiting a key organismal event.

Antibiotic drugs that are widely used have certain dose dependent, tissue specific toxicities. For example renal toxicity is seen with the use of gentamicin, tobramycin, and amphotericin; hepatotoxicity is seen with the use of INH and rifampin; bone

marrow toxicity is seen with chloramphenicol; and platelet toxicity is seen with ticarcillin, etc. These toxicities limit their use. One can introduce candidate bioactive species into the specific cell types where specific changes leading to cellular damage or apoptosis by the antibiotics are produced, and one can screen for bioactive species which confer protection, when these cells are treated with these specific antibiotics.

Furthermore, the present invention finds use in screening for bioactive species that block antibiotic transport mechanisms. The rapid secretion from the blood stream of certain antibiotics limits their usefulness. For example penicillins are rapidly secreted by certain transport mechanisms in the kidney and choroid plexus in the brain. Probenecid is known to block this transport and increase serum and tissue levels. Candidate agents can be introduced into specific cells derived from kidney cells and cells of the choroid plexus known to have active transport mechanisms for antibiotics. One can then screen for bioactive species which block the active transport of specific antibiotics and thus extend the serum halflife of these drugs.

In one embodiment bioactive species obtainable by the methods of the present invention are useful in drug toxicities and drug resistance applications. Drug toxicity is a significant clinical problem. This may manifest itself as specific tissue or cell damage with the result that the drug's effectiveness is limited. Examples include myeloablation in high dose cancer chemotherapy, damage to epithelial cells lining the airway and gut, and hair loss.

Specific examples include adriamycin induced cardiomyocyte death, cisplatinin-induced kidney toxicity, vincristine-induced gut motility disorders, and cyclosporin-induced kidney damage. Candidate bioactive species can be introduced into specific cell types with characteristic drug-induced phenotypic or functional responses, in the presence of the drugs, and one can screen for bioactive agents which reverse or protect the specific cell type against the toxic changes when exposed to the drug. These effects may manifest as blocking the drug induced apoptosis of the cell of interest, thus initial screens will be for survival of the cells in the presence of high levels of drugs or combinations of drugs used in combination chemotherapy.

Drug toxicity can be due to a specific metabolite produced in the liver or kidney which is highly toxic to specific cells, or due to drug interactions in the liver which

block or enhance the metabolism of an administered drug. Candidate bioactive species can be introduced into liver or kidney cells following the exposure of these cells to the drug known to produce the toxic metabolite. One can screen for bioactive species which alter how the liver or kidney cells metabolize the drug, and for bioactive species which prevent the generation of a specific toxic metabolite. The generation of the metabolite can be followed by mass spectrometry, and phenotypic changes can be assessed by microscopy. Such a screen can also be done in cultured hepatocytes, cocultured with readout cells which are specifically sensitive to the toxic metabolite. Applications include reversible (to limit toxicity) inhibitors of enzymes involved in drug metabolism.

Multiple drug resistance, and hence tumor cell selection, outgrowth, and relapse, leads to morbidity and mortality in cancer patients. Candidate bioactive species can be introduced into tumor cell lines (primary and cultured) that have demonstrated specific or multiple drug resistance. One can then screen for bioactive species which confer drug sensitivity when the cells are exposed to the drug of interest, or to drugs used in combination chemotherapy. The readout can be the onset of apoptosis in these cells, membrane permeability changes, the release of intracellular ions and fluorescent markers. The cells in which multidrug resistance involves membrane transporters can be preloaded with fluorescent transporter substrates, and selection carried out for bioactive species which block the normal efflux of fluorescent drug from these cells. Candidate bioactive species are particularly suited to screening for bioactive species which reverse poorly characterized or recently discovered intracellular mechanisms of resistance or mechanisms for which few or no chemosensitizers currently exist, such as mechanisms involving LRP (lung resistance polypeptide). This polypeptide has been implicated in multidrug resistance in ovarian carcinoma, metastatic malignant melanoma, and acute myeloid leukemia. Particularly interesting examples include screening for agents which reverse more than one important resistance mechanism in a single cell, which occurs in a subset of the most drug resistant cells, which are also important targets. Applications would include screening for inhibitors of both MRP (multidrug resistance related polypeptide) and LRP for treatment of resistant cells in metastatic melanoma, for inhibitors of both p-glycopolypeptide and LRP in acute myeloid leukemia, and for inhibition (by any mechanism) of all three polybioactive species for treating pan-resistant cells.

In one embodiment, the bioactive species obtainable by the methods of the present invention are useful in improving the performance of existing or developmental drugs. First pass metabolism of orally administered drugs limits their oral bioavailability, and can result in diminished efficacy as well as the need to administer more drug for a desired effect. Reversible inhibitors of enzymes involved in first pass metabolism may thus be a useful adjunct enhancing the efficacy of these drugs. First pass metabolism occurs in the liver, thus inhibitors of the corresponding catabolic enzymes may enhance the effect of the cognate drugs.

Reversible inhibitors would be delivered at the same time as, or slightly before, the drug of interest. Screening of candidate bioactive species in hepatocytes for inhibitors (by any mechanism, such as polypeptide down regulation as well as a direct inhibition of activity) of particularly problematical isozymes would be of interest. These include the CYP3A4 isozymes of cytochrome P450, which are involved in the first pass metabolism of the anti-HIV drugs saquinavir and indinavir. Other applications could include reversible inhibitors of UDP-glucuronyltransferases, sulfotransferases, N-acetyltransferases, epoxide hydrolases, and glutathione 5-transferases, depending on the drug. Screens would be done in cultured hepatocytes or liver microsomes, and could involve antibodies recognizing the specific modification performed in the liver, or cocultured readout cells, if the metabolite had a different bioactivity than the untransformed drug.

The enzymes modifying the drug would not necessarily have to be known, if screening was for lack of alteration of the drug.

In one embodiment, the bioactive species obtainable by the methods of the present invention are useful in immunobiology, inflammation, and allergic response applications. Selective regulation of T lymphocyte responses is a desired goal in order to modulate immune-mediated diseases in a specific manner. Candidate bioactive species can be introduced into specific T cell subsets (TH1, TH2, CD4+, CD8+, and others) and the responses which characterize those subsets (cytokine generation, cytotoxicity, proliferation in response to antigen being presented by a mononuclear leukocyte, and others) modified by members of the library. One can screen for activities of bioactive species obtainable by the methods of the present invention which increase or diminish the known T cell subset physiologic response. This approach will be useful in any number of conditions, including: 1) autoimmune

diseases where one wants to induce a tolerant state (select a peptide that inhibits T cell subset from recognizing a self-antigen bearing cell); 2) allergic diseases where one wants to decrease the stimulation of IgE producing cells (select peptide which blocks release from T cell subsets of specific Cell stimulating cytokines which induce switch to IgE production); 3) in transplant patients where one wants to induce selective immunosuppression (select peptide that diminishes proliferative responses of host T cells to foreign antigens); 4) in lymphoproliferative states where one wants to inhibit the growth or sensitize a specific T cell tumor to chemotherapy and/or radiation; 5) in tumor surveillance where one wants to inhibit the killing of cytotoxic T cells by Fas ligand bearing tumor cells; and 5) in T cell mediated inflammatory diseases such as Rheumatoid arthritis, Connective tissue diseases (SLE), Multiple sclerosis, and inflammatory bowel disease, where one wants to inhibit the proliferation of disease-causing T cells (promote their selective apoptosis) and the resulting selective destruction of target tissues (cartilage, connective tissue, oligodendrocytes, gut endothelial cells, respectively).

Regulation of B cell responses will permit a more selective modulation of the type and amount of immunoglobulin made and secreted by specific B cell subsets. Candidate bioactive species can be introduced into B cells and one can screen for activities of bioactive species which inhibit the release and synthesis of a specific immunoglobulin. This can be useful in autoimmune diseases characterized by the overproduction of auto antibodies and the production of allergy causing antibodies, such as IgE. One can also screen for bioactive species which inhibit or enhance the binding of a specific immunoglobulin subclass to a specific antigen either foreign of self. Finally, one can screen for bioactive species which inhibit the binding of a specific immunoglobulin subclass to its receptor on specific cell types.

Similarly, one can screen for bioactive agents which affect cytokine production, generally by using two cell systems. For example, cytokine production from macrophages, monocytes, etc. can be evaluated. Similarly, one can screen for bioactive species which mimic cytokines, for example erythropoetin and IL1-17, or for bioactive species that bind cytokines such as TNF-alpha, before they bind their receptor.

Antigen processing by mononuclear leukocytes (ML) is an important early step in the immune system's ability to recognize and eliminate foreign polybioactive

species. Candidate bioactive species can be introduced into ML cell lines and one can screen for bioactive species which alter the intracellular processing of foreign bioactive species and sequence of the foreign peptide that is presented to T cells by MLs on their cell surface in the context of Class II MHC. One can look for members of a library of bioactive species which enhance immune responses of a particular T cell subset (for example, the peptide would in fact work as a vaccine), or look for a bioactive species library member that binds more tightly to MHC, thus displacing naturally occurring bioactive species, but nonetheless the bioactive species would be less immunogenic (less stimulatory to a specific T cell clone). Such bioactive species would in fact induce immune tolerance and/or diminish immune responses to foreign agents, such as polypeptides. This approach could be used in transplantation, autoimmune diseases, and allergic diseases.

The release of inflammatory mediators (cytokines, leukotrienes, prostaglandins, platelet activating factor, histamine, neurobioactive species, and other peptide and lipid mediators) is a key element in maintaining and amplifying aberrant immune responses. Candidate bioactive species can be introduced into MLs, mast cells, eosinophils, and other cells participating in a specific inflammatory response, and one can screen for bioactive species which inhibit the synthesis, release and binding to the cognate receptor of each of these types of mediators.

In one embodiment, the bioactive species obtainable by the methods of the present invention are useful in biotechnology applications. Random bioactive species displayed on the surface of circulating cells can be used as tools to identify organ, tissue, and cell specific targeting sequences. Any cell introduced into the bloodstream of an animal expressing a library targeted to the cell surface can be selected for specific organ and tissue targeting. The bioactive species identified in this way can then be coupled to an antibody, enzyme, drug, imaging agent or substance for which organ targeting is desired.

Other bioactive species for which screens can be set up include: 1) bioactive species which block e.g. the activity of transcription factors, using cell lines with reporter genes; 2) bioactive species which block the interaction of two known biological molecules in cells, using the absence of normal cellular functions, the mammalian two-hybrid system or fluorescence resonance energy transfer mechanisms for detection.

Enrichment

The present invention also relates to a method for determining the identity of a chemical entity having a preselected property, comprising the steps of:

i) generating a tagged library of chemical entities by appending unique identifier tags to chemical entities,

ii) subjecting the library to a condition, wherein a chemical entity or a subset of chemical entities having a predetermined property is partitioned from the remainder of the library,

iii) recovering an anti-tag from the partitioned library, said anti-tag being capable of interacting with the unique identifier tag in a specific manner, and

iv) identifying the chemical entity/ies having a preselected function by decoding the anti-tag.

The tag is appended the chemical entity by a suitable process. Notably, each chemical entity is appended a tag by a reaction involving a chemical reaction between a reactive group of the chemical entity and a reactive group of the tag, such as method A and B of the selection section. The attachment of the chemical entity can be directly or through a bridging molecule part. The molecule part can be any suitable chemical structure able to connect the chemical entity to the tag.

The anti-tag has the ability to interact with the unique identifier tag in a specific manner. The chemical structure of the anti-tag is to a large extent dependant on the choice of unique tag. As an example, if the unique tag is chosen as an antibody, the anti-tag is selected as the epitope able to associate with the antibody. In general, it is preferred to use an anti-tag comprising a sequence of nucleotides complementary to a unique identifier tag.

The method can be performed without amplification in certain embodiments. However, when larger bioactive species are intended, it is in general preferred to use an anti-tag which is amplifiable. Anti-tags comprising a sequence of nucleotides can be amplified using standard techniques like PCR.

In the event the tag as well as the anti-tag is a sequence of nucleic acids, a tag:anti-tag hybrid can be formed prior to the subjecting the library to partitioning conditions or subsequent to the partitioning step. In some embodiments of the invention it is preferred to form the tag:anti-tag hybrid prior to the partition step in order to make

the appended nucleotide sequence inert relative to the system as it is well known that certain sequences of nucleotides can bind to a target or catalyse a chemical reaction.

The oligonucleotide anti-tag can be formed in a variety of ways. In one embodiment of the invention, the anti-tag is formed as an enzymatic extension reaction. The extension comprises the initial annealing of a primer to the unique identifier tag and subsequent extension of the primer using a polymerase and dNTPs. Other types of extension reactions may also be contemplated. As an example ligases can be used to create the primer starting from di- or trinucleotide substrates and the extension can be performed using a suitable polymerase.

It can be desirable to recover the anti-tag at various steps during the process. To this end it is preferred in some aspects of the invention to provide the primer provided with a chemical entity capable of binding to a suitable affinity partner. An arsenal of different chemical entities and affinity partners are available to the skilled person in the art. The most widely used chemical entity is biotin, which in general are also preferred according to the present invention. Biotin binds to the affinity partner streptavidin or avidin. A standard technique in the laboratory is to recover a biochemical entity having attached a biotin using a solid phase covered with streptavidin. Suitably, the solid phase is a bead which can be separated from the liquid after the binding action by rotation or a magnetic field in case the solid bead comprises magnetic particles.

In other aspects of the present invention, the anti-tag is provided as a separate oligonucleotide. The separate oligonucleotide can be produced using standard amidite synthesis strategies or can be provided using other useful methods. It is in general preferred to provide the oligonucleotide by synthesis, at least in part, because the biotin amidite is easily incorporated in a nascent oligonucleotide strand. Following the addition of an oligonucleotide anti-tag to a liquid comprising chemical entities tagged with complementing oligonucleotide tags a double stranded library is formed as a hybridisation product between the unique identifier tag and the anti-tag oligonucleotide.

As mentioned above, the anti-tag oligonucleotide can be provided with a chemical entity, such as biotin, capable of binding to an affinity partner, such as streptavidin or avidin.

Following the addition of the anti-tag oligonucleotides to the tagged chemical entities, some of the oligonucleotides present in the media may not find a partner. In one embodiment of the invention it is preferred that oligonucleotides not hybridised to a cognate unique identifier and/or anti-tag are transformed into a double helix. In other aspects of the invention single stranded oligonucleotides are degraded prior to step ii) to avoid unintended interference.

The chemical entity can be used to purify the library prior to or subsequent to the partitioning step. In some embodiments of the invention, the purification step is performed prior to the partitioning step to reduce the noise of the system. In another aspect the chemical entity is used to purify the partitioned library subsequent to step ii) in order to recover a double stranded product which can be amplified.

The library is subjected to a condition in order to select chemical entities having a property which is responsive to this condition. The condition may involve the exposure of the library to a target and partitioning the chemical entities having an affinity towards this target. Another condition could be subjecting the library to a substrate and partitioning chemical entities having a catalytical activity relative to this substrate.

The anti-tag can be formed subsequent to the partitioning step. In an aspect of the invention, the single stranded nucleotide serving as a tag is made double stranded while the chemical entity is attached to the target of an affinity partitioning. Optionally, in a repeated temperature cycle, a plurality of anti-tags can be formed as extension products using the tag as template. In another aspect of the invention, the chemical entity bearing the single stranded oligonucleotide is detached from the target and a complementing anti-tag is subsequently prepared.

In the event the anti-tag comprises a chemical entity, this chemical entity can be used to purify the partitioned library. The recovery of the anti-tag is then performed by melting off said anti-tag from a partitioned double stranded library. Optionally, the

amount of anti-tags can be multiplied by conventional amplification techniques, such as PCR.

The method according to the invention can be performed using a single partitioning step. Usually, it is preferred, however, to use more than one partitioning step in order to select the candidate having the desired properties from a large library. Thus, the recovered anti-tags can be mixed with the initial library or a subset thereof and the steps of partitioning (step ii)) and recovery (step iii)) may is repeated a desired number of times. Optionally, single stranded moieties in the mixture can be degraded or removed or made inert as described above.

Generally, the partitioned library obtained in step ii) is subjected to one or more further contacting steps using increasing stringency conditions. The stringency conditions can be increased by increasing the temperature, salt concentration, acidity, alkalinity, etc.

In one embodiment of the invention, the partitioned library is not subjected to intermediate process steps prior to a repeated contacting step. Especially, the partitioned library is not subjected to intermediate amplification of the anti-tag. This embodiment can be of advantage when relatively small bioactive species are used.

The method of the invention terminates with a decoding step, that is a step in which the identity of the chemical entity or entities are deciphered by an analysis of the anti-tag. When the anti-tag is an oligonucleotide, the decoding step iv) can be performed by sequencing an anti-tag nucleotide. Various methods for sequencing are apparent for the skilled person, including the use of cloning and exposure to a microarray.
The tags contain recognizing groups such as e.g. nucleotide sequence(s), epitope(s) a.o. The tags carries information of the entity to which it is attached, such as e.g. entity structure, mass, spatial position (plate information) etc. The tags can be composed of monoclonal antibodies, bioactive species, proteins, oligonucleotides, DNA, RNA, LNA, PNA, natural bioactive species, unnatural bioactive species, polymeric or oligomeric hydrazino aryl and alkyl carboxylic acids, polymeric or oligomeric aminoxy aryl and alkyl carboxylic acids, peptoids, other natural polymers or oligomers, unnatural polymers (molecular weight > 1000 Da) or

oligomers (molecular weight < 1000 Da), small non-polymeric molecules (molecular weight < 1000 Da) or large non-polymeric molecules (molecular weight > 1000 Da).

In one embodiment, entities consist of small non-polymeric molecules (molecular weight < 1000 Da). Small molecules are generally the compounds of interest in the quest for drug oral candidates. Especially, small molecules not occurring in Nature are of interest in the drug discovery process and in one embodiment of the present invention the method are designed to select a oral drug candidate. A variety of drug candidate bioactive species are available on the market. The drug candidates of the library usually comprise a reactive group or a group which can be altered into a reactive group. In one preferred aspect of the present invention each of the members of the drug candidate library is appended a nucleic acid tag via said reactive group of the library member and a reactive group on the nucleic acid. Preferably, the nucleic acid is an oligonucleotide.

In another aspect of the invention, entities consist of large non-polymeric molecules (molecular weight > 1000 Da). In still another embodiment, entities consist of polymeric molecules.

The tags and anti-tags can be composed of RNA linked to monoclonal antibodies, proteins, LNA, PNA, natural polybioactive species, unnatural polybioactive species, polymeric or oligomeric hydrazino aryl or alkyl carboxylic acids, polymeric or oligomeric aminoxy aryl or alkyl carboxylic acids, other natural polymers or oligomers, unnatural polymers (molecular weight > 1000 Da) or oligomers (molecular weight < 1000 Da), small non-polymeric molecules (molecular weight < 1000 Da) or large non-polymeric molecules (molecular weight > 1000 Da).

Alternatively, anti-tags can be composed of DNA linked to monoclonal antibodies, proteins, LNA, PNA, natural polybioactive species, unnatural polybioactive species, polymeric or oligomeric hydrazino aryl or alkyl carboxylic acids, polymeric or oligomeric aminoxy aryl or alkyl carboxylic acids, other natural polymers or oligomers, unnatural polymers (molecular weight > 1000 Da) or oligomers (molecular weight < 1000 Da), small non-polymeric molecules (molecular weight < 1000 Da) or large non-polymeric molecules (molecular weight > 1000 Da).
Alternatively, anti-tags are just composed of oligonucleotides, DNA or RNA. In a

embodiment, anti-tags are composed of DNA. In another embodiment anti-tags are composed of RNA.

Anti-tags which are linked to DNA or RNA are also encoded by the DNA/RNA linked to them, e.g. phage displayed or polysome displayed antibodies, bioactive species or proteins, and via DNA-templated synthesis of anti-tags, where the DNA encode the synthesis of the anti-tag, which is linked to its DNA during its synthesis.

Each chemical compound or group of compounds can be associated with a tag through formation of a covalent or non-covalent bond. For covalent bond formation, tagging may involve, but is not limited to, the formation of a cycloaddition product, an alkylation product, an arylation product, an acylation product, an amide bond, a carboxylic ester bond, a sulfonamide bond, a disulfide bond, an S-alkyl bond, an NR-alkyl bond, an O-alkyl bond, an aryl-vinyl bond, an alkyne-vinyl bond, an oxime bond, an imine bond, a bicyclic product, a trizole, a hexene, a 7-Oxa-bicyclo[2.2.1]hept-2-ene derivative, a 7-Aza-bicyclo[2.2.1]hept-2-ene derivative or a 7-Methyl-7-aza-bicyclo[2.2.1]hept-2-ene. Non-covalent bonds may involve, but are not limited to, attachment via e.g. hydrogen bonding, van der Waals interactions, pi-stacking or through hybridization. Hybridization can be between complementary strands of DNA, RNA, PNA or LNA or mixtures thereof. In such case both the tag and the chemical compound carries such a strand complementary to each other. The tagged entity, compound or mixture of compounds can be transformed into a new tagged entity, e.g. by transformation of the entity or by transformation of the tag. The transformation can be caused by either chemical or physical transformations such e.g. addition of reagents (e.g. oxidizing or reducing agents, pH adjustment a.o.) or subjection to UV-irradiation or heat.

The complex between tags and anti-tags can be formed on individually tagged entities immediately after tagging. Alternatively, after mixing individually tagged entities, either before or after the optionally use of library purification, or either before or after library enrichment for specific properties.
When tags and anti-tags are composed of nucleotides the complex consists of a double stranded nucleotide, e.g. duplex DNA or hybrids DNA/RNA.

The purification chemical entity (denoted "@") can be connected to the anti-tag. The purification chemical entity contains a recognizing group(s) such as e.g. nucleotide

sequence(s), epitopes, reactive groups, high affine ligands a.o. The purification chemical entities can be composed of monoclonal antibodies, bioactive species, proteins, DNA, RNA, LNA, PNA, natural bioactive species, unnatural bioactive species, polymeric or oligomeric hydrazine aryl or alkyl carboxylic acids, polymeric or oligomeric aminoxy aryl or alkyl carboxylic acids, other natural polymers or oligomers, unnatural polymers (molecular weight > 1000 Da) or oligomers (molecular weight < 1000 Da), small non-polymeric molecules (molecular weight < 1000 Da) or large non-polymeric molecules (molecular weight > 1000 Da). Purification chemical entities may e.g. be a nucleotide sequence, biotin, streptavidin, avidin, “his-tags”, mercapto groups or disulfide/activated disulfide groups. The purification chemical entity can be part of the anti-tag, e.g. in the case the anti-tag is nucleotide based or e.g. antibodies where part of the antibody may serve as epitop for another antibody (e.g. immobilized antibody which serve as purification filter).

Purification filters contains components which associate, interact or react with purification chemical entities whereby a complex is formed. This complex allows separation of non-complexed tagged entities and complexed tagged entities. The purification filter contains a recognizing group(s) such as e.g. nucleotide sequence(s), epitopes, reactive groups, high affine ligands a.o. The purification filter can be composed of monoclonal antibodies, bioactive species, proteins, DNA, RNA, LNA, PNA, natural bioactive species, unnatural bioactive species, polymeric or oligomeric hydrazino aryl or alkyl carboxylic acids, polymeric or oligomeric aminoxy aryl or alkyl carboxylic acids, other natural polymers or oligomers, unnatural polymers (molecular weight > 1000 Da) or oligomers (molecular weight < 1000 Da), small non-polymeric molecules (molecular weight < 1000 Da) or large non-polymeric molecules (molecular weight > 1000 Da). Purification filters may e.g. be a nucleotide sequence, biotin, strepdavidin, avidin, “his-tags”, mercapto groups or disulfide/activated disulfide groups.

The library is probed and enriched for properties. Properties can be affinity, catalytic activity or membrane penetrating capability a.o.

Amplification may use PCR or RTPCR techniques. Anti-tags are amplifiable in some aspects of the invention. Anti-tags can be separated from tags by use of physical or chemical means, such as e.g. UV-irradiation, heat, pH-adjustment, use of salt solutions a.o.

Isolated tagged entities can be identified either trough their tag or anti-tag. Identification can be accomplished by cloning of anti-tags and sequencing their DNA/RNA or through mass analysis of either tagged entities or anti-tags or complexes of anti-tags/tagged entities.

The library of tagged entities may involve $10\text{-}10^{20}$ or $10\text{-}10^{14}$ or $10\text{-}10^{2}$ or $10\text{-}10^{3}$ or $10^{2}\text{-}10^{3}$ or $10^{2}\text{-}10^{4}$ or $10^{3}\text{-}10^{6}$ or $10^{3}\text{-}10^{8}$ or $10^{3}\text{-}10^{10}$ or $10^{3}\text{-}10^{14}$ or $10^{5}\text{-}10^{6}$ or $10^{5}\text{-}10^{8}$ or $10^{5}\text{-}10^{10}$ or $10^{5}\text{-}10^{14}$ or $10^{8}\text{-}10^{14}$ or $10^{14}\text{-}10^{20}$ entities.

Library complexes of tagged entities and anti-tags can be enriched for properties prior to purification by use of purification chemical entity and purification filter or after purification.

The term unique, when used together with sequences of nucleotides, implies that at least one of the nucleobases and/or backbone entities of the sequence does not appear together with different chemical entities. Preferably, a specific sequence is unique due to fact that no other chemical entities are associated with the same sequence of nucleobases.

Once the library has been formed, one must screen the library for chemical compounds having predetermined desirable characteristics. Predetermined desirable characteristics can include binding to a target, catalytically changing the target, chemically reacting with a target in a manner which alters/modifies the target or the functional activity of the target, and covalently attaching to the target as in a suicide inhibitor.

The target can be any compound of interest. The target can be a protein, peptide, carbohydrate, polysaccharide, glycoprotein, hormone, receptor, antigen, antibody, virus, substrate, metabolite, transition state analog, cofactor, inhibitor, drug, dye, nutrient, growth factor, cell, tissue, etc. without limitation. Particularly preferred targets include, but are not limited to, angiotensin converting enzyme, renin, cyclooxygenase, 5-lipoxygenase, IIL- 1 0 converting enzyme, cytokine receptors, PDGF receptor, type II inosine monophosphate dehydrogenase, ß-lactamases, and fungal cytochrome P-450. Targets can include, but are not limited to, bradykinin, neutrophil elastase, the HIV proteins, including *tat, rev, gag, int,* RT, nucleocapsid

etc., VEGF, bFGF, TGFß, KGF, PDGF, thrombin, theophylline, caffeine, substance P, IgE, sPLA2, red blood cells, glioblastomas, fibrin clots, PBMCs, hCG, lectins, selectins, cytokines, ICP4, complement proteins, etc.

The stringency conditions under which the library are screened are normally limited to such condition that maintain the hybridisation between the identifier tag and the anti-tag. High stringency conditions can be applied, however, followed by a renewed synthesis or attachment of the anti-tag. Screening conditions are known to one of ordinary skill in the art.

Chemical compounds having predetermined desirable characteristics can be partitioned away from the rest of the library while still attached to a nucleic acid identifier tag by various methods known to one of ordinary skill in the art. In one embodiment of the invention the desirable products are partitioned away from the entire library without chemical degradation of the attached nucleic acid such that the identifier nucleic acids are amplifiable. The identifier tag may then be amplified, either still attached to the desirable chemical compound or after separation from the desirable chemical compound.

In the most embodiment, the desirable chemical compound acts on the target without any interaction between the tag attached to the desirable chemical compound and the target. In one embodiment, the desirable chemical compounds bind to the target and the bound tag-desirable chemical compound-target complex can be partitioned from unbound products by a number of methods. The methods include nitrocellulose filter binding, column chromatography, filtration, affinity chromatography, centrifugation, and other well known methods.

Briefly, the library is subjected to the partitioning step, which may include contact between the library and a column onto which the target is bound. All tags which have not formed hybridisation products with a chemical entity-tag aggregate or those tags associated with undesirable chemical entities will pass through the column. Additional undesirable chemical entities (e.g., entities which cross-react with other targets) can be removed by counter-selection methods. Desirable complexes are bound to the column and can be eluted by changing the conditions of the column (e.g., salt, etc.) or the tag associated with the desirable chemical compound can be cleaved off and eluted directly.

Additionally, chemical compounds which react with a target can be separated from those products that do not react with the target. In one example, a chemical compound which covalently attaches to the target (such as a suicide inhibitor) can be washed under very stringent conditions. The resulting complex can then be treated with proteinase, DNAse or other suitable reagents to cleave a linker and liberate the nucleic acids which are associated with the desirable chemical compound. The liberated nucleic acids can be amplified.

In another example, the predetermined desirable characteristic of the desirable product is the ability of the product to transfer a chemical group (such as acyl transfer) to the target and thereby inactivate the target. One could have a product library where all of the products have a thioester chemical group. Upon contact with the target, the desirable products will transfer the chemical group to the target concomitantly changing the desirable product from a thioester to a thiol. Therefore, a partitioning method which would identify products that are now thiols (rather than thioesters) will enable the selection of the desirable products and amplification of the nucleic acid associated therewith.

There are other partitioning and screening processes which are compatible with this invention that are known to one of ordinary skill in the art. In one embodiment, the products can be fractionated by a number of common methods and then each fraction is then assayed for activity. The fractionization methods can include size, pH, hydrophobicity, etc.

Inherent in the present method is the selection of chemical entities on the basis of a desired function; this can be extended to the selection of small molecules with a desired function and specificity. Specificity can be required during the selection process by first extracting identifier sequences of chemical compounds which are capable of interacting with a non-desired "target" (negative selection, or counter-selection), followed by positive selection with the desired target. As an example, inhibitors of fungal cytochrome P-450 are known to cross-react to some extent with mammalian cytochrome P-450 (resulting in serious side effects). Highly specific inhibitors of the fungal cytochrome could be selected from a library by first removing those products capable of interacting with the mammalian cytochrome, followed by retention of the remaining products which are capable of interacting with the fungal

cytochrome.

Following the selection procedure, anti-tags are recovered. The recovery can be performed by subjecting the selected complexes to stringency conditions which will detach the anti-tag sequences from the identifier tag. In the event the tag and the anti-tag are nucleic acids, the stringency conditions can be increased by increasing the temperature gradually until the two strands of the double helix are melted apart. Further copies of anti-tag sequences can be provided by extension of the identifier sequences using a suitable primer and a polymerase. In the alternative, the recovered anti-tag sequence and/or the identifier sequence tag can be subjected to PCR to form a double stranded product. The strands comprising the sequence that complements at least a part of a unique identifier sequence are subsequently isolated.

The selected chemical entity can be attached to the target during the extension or amplification or can be detached from the target. In one embodiment of the invention, it is preferred that the target is immobilised and the chemical compound remain attached to the target during the extension or amplification, to allow for easy recovery of the extension or amplification product by simple elution. In another aspect the selected chemical entities are separated from the unique identifier sequences, prior to, simultaneous with or subsequent to the recovery of the enrichment sequences.

In order to recover the desired anti-tag sequences, it can be appropriate to provide the native as well as the amplified, if present, anti-tag sequences with one part of a molecular affinity pair. The one part of a molecular affinity pair is also referred to herein as a chemical entity. The anti-tags may then be recovered by using the other part of the molecular affinity pair attached to a solid phase, which is possible to isolate. The essential property of the molecular affinity pair is that the two parts are capable of interacting in order to assemble the molecular affinity pair. In the biotechnological field a variety of interacting molecular parts are known which can be used as the molecular affinity pair. Examples include, but are not restricted to protein-protein interactions, protein-polysaccharide interactions, RNA-protein interactions, DNA-DNA interactions, DNA-RNA interactions, RNA-RNA interactions, biotin-streptavidin interactions, enzyme-ligand interactions, antibody-ligand interaction, protein-ligand interaction, ect.

A suitable molecular affinity pair is biotin-streptavidin. The anti-tag sequences can be provided with biotin, e.g. by using a primer attached to a biotin moiety in the amplification or extension step and contacting the biotin tagged anti-tag sequence with beads coated with streptavidin.

After the recovery of the anti-tag sequences, these are contacted with the initial library or a fraction thereof and an enriched library is allowed to be formed by the hybridisation of the anti-tag sequences to the cognate sequence of the unique identifier tag.

The method according to the invention can be repeated one or more times. In a second round of the method, the part of the single stranded library not recognized by an anti-tag sequence can be cleared from the reaction media or the remaining part of the single stranded library may remain in admixture with the enrich library. In general, it is not necessary to separate the remaining part of the single stranded library from the media before the enriched double stranded library is subjected to a second contact with the target because conditions for the preselected function usually are more stringent than the first round, wherefore the members of the single stranded library presumably will not bind to the target. However, to reduce the noise of the system, it can be useful at some events to withdraw from the media the members of the single stranded initial library not mated with an anti-tag sequence. If the anti-tag sequences are provided with one part of a molecular affinity pair, like biotin, the chemical compounds of interest can be extracted from the media by treatment with immobilized streptavidin, e.g beads coated with streptavidin.

As mentioned above, the conditions for performing the second or further selection step is generally more stringent than in the first or preceding step. The increasing stringency conditions in sequential selection rounds provide for the formation of a sub-library of chemical compounds which is narrowed with respect to the number but enriched with respect to the desired property.

In the present description with claims, the terms nucleic acid, oligonucleotide, oligo, and nucleotides are used frequently. The terms nucleotide, nucleotide monomer, or mononucleotides are used to denote a compound normally composed of two parts, namely a nucleobase moiety, and a backbone. The back bone may in some cases

be subdivided into a sugar moiety and an internucleoside linker. Mononucleotides can be linked to each other to form a oligonucleotide. Usually, the mononucleotides are linked through an internucleoside linkage. The term nucleic acid covers mononucleotides as well as oligonucleotides. Usually, however, the term denotes an oligonucleotide having from 2 to 30 mononucleotides linked together through internucleoside linkers.

Determining the identifier oligonucleotide of the bifunctional complex

The identifier oligonucleotide of the identifier sequence present in the isolated bifunctional molecules or the separated identifier oligonucleotides is determined to identify the chemical entities that participated in the formation of the molecule. The synthesis method of the molecule can be established if information on the functional entities as well as the point in time they have been incorporated in the molecule can be deduced from the identifier oligonucleotide. It can be sufficient to get information on the chemical structure of the various chemical entities that have participated in the molecule to deduce the full molecule due to structural constraints during the formation. As an example, the use of different kinds of attachment chemistries may ensure that a chemical entity on a reactant can only be transferred to a single position on a scaffold. Another kind of chemical constrains can be present due to steric hindrance on the scaffold molecule or the functional entity to be transferred. In general however, it is preferred that information can be inferred from the identifier sequence that enable the identification of each of the chemical entities that have participated in the formation of the molecule along with the point in time in the synthesis history the chemical entities have been incorporated in the (nascent) molecule.

Although conventional DNA sequencing methods are readily available and useful for this determination, the amount and quality of isolated bifunctional molecule may require additional manipulations prior to a sequencing reaction.

Where the amount is low, it is preferred to increase the amount of the identifier sequence by polymerase chain reaction (PCR) using PCR primers directed to primer binding sites present in the identifier sequence.

In addition, the quality of the isolated bifunctional molecule can be such that multiple species of bifunctional molecules are co-isolated by virtue of similar capacities for

binding to the target. In cases where more than one species of bifunctional molecule are isolated, the different isolated species must be separated prior to sequencing of the identifier oligonucleotide.

Thus in one embodiment, the different identifier sequences of the isolated bifunctional complexes are cloned into separate sequencing vectors prior to determining their sequence by DNA sequencing methods. This is typically accomplished by amplifying all of the different identifier sequences by PCR as described herein, and then using a unique restriction endonuclease sites on the amplified product to directionally clone the amplified fragments into sequencing vectors. The cloning and sequencing of the amplified fragments then is a routine procedure that can be carried out by any of a number of molecular biological methods known in the art.

Alternatively, the bifunctional complex or the PCR amplified identifier sequence can be analysed in a microarray. The array can be designed to analyse the presence of a single tag or multiple tags in an identifier sequence.

Examples

General procedures

The following general procedures were used to synthesize libraries. For example one general procedure used is the reaction of a reactant with a reactive site. Another general procedure used is the attachment of a tag to a nascent bifunctional complex. Yet another general procedure used is a purification of a nascent bifunctional complex or a quenching of a reactive site, e.g. by reaction with a reactant such that the reactive site was rendered unreactive. It is to be understood that any variable such as volume, amount, temperature, pressure, number, concentration, solvent type, reactant type, and composition described in the

following general procedures can be varied according to specific needs. It is to be understood that the results obtained by these general procedures can be achieved with a vast number of other variant procedures.

General procedures containing a volume reduction step:

V1) Volume reduction by lyophilization

The contents of wells were lyophilized in a speed vac

V2) Volume reduction by precipitation

The sample was precipitated using 0.1 volumes of 5 M NaCl and 0.5 volumes of isopropanol or 1.5 volumes of ethanol and washed with cold 70% ethanol. A sample of the material was analysed by polyacrylamide gel electrophoresis and autoradiography to verify the efficiency of dephosphorylation.

General procedures containing a splitting step:

S1) The total pool or a part of the pool the total pool was split equally in 1-10.000 wells, e.g. 8, 16, 24, 32, 40, 48, 56, 64, 72, 80, 88, 96, 192, 384, or 1536 wells.

General procedures containing a mixing step include:

M1) The contents of all wells were mixed to form one pool

M2) Different pools were formed by mixing the contents of different wells

General procedures modifying a reactant

B1) Method for generating an aliphatic aldehyde

The material was redissolved in 25 µl NaIO4 (50 mM in Sodium Acetate Buffer pH 4 and shaken at 25oC for 30 min. 25 µl 700mM Phosphate buffer pH 6.7 was added.

General procedures containing a reaction of a reactant with a reactive site:

R1) Reactants containing an acid which reacts with an amine forming an amide bond:

Bifunctional complexes were distributed to wells. Samples to undergo acylation were dissolved in 5 µl 200 mM Na-phosphate buffer pH 8.0 or 100 mM Na-Borate pH 9.0 or 100 mM Na-Borate pH 10.0. Then, 4 µl specific reactant (100 mM in dimethylsulfoxide) was added to each well. Then 1 µl DMT-MM mix (0.36 M DMT-

MM in water and 56 mM Na-phosphate buffer pH 8) was mixed in each well and the sample was incubate at 30° C for 16 hours.

R2) Reactants containing an isocyanate which can react with an amine forming an urea bond:
Lyophilize the contents of all wells. Mix 2ml 100mM Na-Borate buffer pH 8, with 2ml 100mM Na-phosphate buffer, pH 8. Add 8 µl buffer mix to each well. Add 1 µL specific BB in 300mM CH3CN to each well. Mix contents of each well. Incubate at 50 degrees celcius for 16 hours.

R3) Reactants containing a sulfonyl group which can react with an amine forming a sulphonamide bond:
Samples to undergo sulfonylation were dissolved in 8 µl 100 mM Sodium Borate buffer pH 9. 2 µl specific reactant (100 mM in tetrahydrofuran) was then to each well and incubated at 30°C for 16 hours.

R4) Reactants containing an aldehyde group which can react with a primary amine forming a secondary amine or with a secondary amine forming a tertiary amine:
Samples to undergo reductive amination were dissolved in 15 µl 200 mM NaOAc buffer pH 5.0 5 ul specific BB was added to each well (200 mM in DMSO) and incubate at 30°C for 1 h. Then 5 µl of freshly prepared 140 mM NaCNBH3 (REA000025; 8.8 mg/ml) in NaOAc buffer pH 5.0 to was added each well and the samples were incubated at 30°C for 16 hours in a PCR-machine. Then 25 µl water was added to each sample.

R5) Reactants containing a halogenated heteroaromatic moiety which can react with an amine forming a C-N bond.
Samples to undergo nucleophilic aromatic substitution were dissolved in 12 µl 100 mM Borate Buffer pH 9. Then 12 µl specific BB was added to each well (100 mM in DMSO) and all wells were incubated for 16 hours at 90°C. Then, 40 µl water was added to each sample.

R6) Reactants containing an amine which can react with an acid forming an amide bond.

The material was redissolved in 10µl H2O. 15µl 100mM Sulfo-NHS in water and 15µl 100mM EDC in water was added. The mixture was shaken at 25°C for 15min. The material was purified in a spin column equilibrated water directly into 15µl 100mM BB/RE in 100 mM sodium phosphate buffer pH 8.0. The mixture was shaken for 45min at 50°C or 16 hours at 37°C.

R7) Reactants containing an amine which can react with an acid forming an amide bond.
The material was redissolved in 35µl 100mM sodium phosphate buffer pH 8.0. 10µl 100mM bulding block solution in water or DMSO was added. 5.0µl 500mM DMT-MM in water was added. The mixture was incubated at 30°C for 2-24 hours.

R8) Reactants containing an aldehyde group which can react with a primary amine forming a secondary amine or with a secondary amine forming a tertiary amine. The reaction being performed in organic solvent (MeOH).
The material was applied to a DEAE (Diethyl aminoethyl) column which had been washed 2 times with 10 mM Aq. AcOH. The material on DEAE was washed with water followed by washing with MeOH. 10 µL 100mM BB in DMSO and 40 µL MeOH (dry) was added and the mixture was shaken at 600 rpm for 1h at 30 °C. 10 µl $NaCNBH_3$ solution (140 mM in MeOH, freshly prepared) was added and the mixture was shaken overnight at 30 °C. The material was then released from DEAE by adding 70 µl Release solution (1.5 M NaCl) and incubating at 25°C for 10 minutes in an eppendorph thermoshaker at 600 rpm. Water was added to the material to a final NaCl concentration of 0.5 M. Then the material was precipitated by adding one volume of isopropanol as described.

General procedures including enabling or including a quality control step:
QC1) Quality control of reactant reaction, e.g. reaction with an identifier oligo
Before a reactant reaction step, 10 µL of spike1 oligo [6TCAAGGAAGTAGGTCACGTA, where 6 is 6 = 5' C2OC2 aminomodifier, Glen research 10-1905] was added to specific wells. After a reactant reaction step 2 µL sample was taken from specific wells and transferred to a 96-well plate. 50 µL buffer which is compatible with mass spectrometry analysis was added. A Mass

spectrometry analysis was performed of the sample(s). The yield of a reaction of a reactant with a reactive site was thus evaluated.

QC2) Quality control of tag addition

At some point during library synthesis tags labelled with a 5' phosporus-32 was added to specific wells. Then, prior to performing a tag addition step samples were taken from a number of wells. These samples were pooled to serve as a marker before tag addition. Following a tag addition, a 0.2mm 10% PAGE gel was prepared and 0.5 µL samples were taken from a number of wells. PAGE loading buffer was added to the samples. The samples were processed by PAGE including a molecular weight marker suitably labelled. The gel was transferred to a support, wrapped in plastic, placed on film, exposed and developed. The efficiency of the tag addition (ligation) step was evaluated by comparing samples taken before and after tag addition.

QC3) Quality control of reactant reaction

Before a reactant reaction step, 10 µL of spike1 oligo [6TCAAGGAAGTAGGTCACGTA, where 6 is 6 = 5' C2OC2 aminomodifier, Glen research 10-1905] was added to specific wells. After a reactant reaction step. Contents of selected wells were added to 50 µL prewashed streptavidin sepharose. The spike1 oligo was captured by adding 500 pmol antispike1. (5TACGTGACCTACTTCCTTGA, where 5 is 5 = 5' Biotin-c6-) and incubating for 5 minutes at 30 degrees celcius. The sample was centrifuged for 1 minute. The flowthrough was removed and added back it to its well of origin. The streptavidin sepharose was washed 1x with 500 µL 25mM NH4Ac pH7.5 and 2 times with 500 µL dH2O. The spike 1 oligo was eluted from the streptavidin sepharose (elution repeated 2 times) with 40µL dH2O heated to 80 degrees celcius. The samples were purified e.g. using P6 [Biorad] and 10-20 µl was used for mass spectrometry analyses as described in general procedure QC2. The efficiency of reactant reactions could thus be determined.

QC4) Quality control of a step which removes tag or renders them unfunctional

Following the termination of a tag addition step, a specific tag (optionally with its anti-tag) was added. After library synthesis, library screening, tags were investigated for the presence of the specific tag which would indicate that a purification following the addition of that specific tag was not efficient.

General procedures containing a purification step:

P1) Purification by size-exclusion chromatography

1 mL of washed P6 slurry was added to the wells of a filter plate (Whatman Unifilter 96 well plates). The filter was placed on a 2mL collection plate and centrifuged for 4 minutes. The filterplate was placed on a collection plate (Eppendorff). The volume of samples to be purified was adjusted to 20-70 µl. The SEC plate on top of the collection plate was centrifuged 4 minutes at 900 x RCF.

P2) Purification by precipitation

The sample was precipitated using 0.1 volumes of 5 M NaCl and 0.5 volumes of isopropanol or 1.5 volumes of ethanol and washed with cold 70% ethanol. A sample of the material was analysed by polyacrylamide gel electrophoresis and autoradiography to verify the efficiency of dephosphorylation.

P3) PAGE gel purification

A 0.2, 1, or 2 mm thickness 6% or 10% acrylamide PAGE gel was prepared. A gel prerun was performed for 1h at 60w. PAGE Loading buffer was added to the material to be purified and denatured by incubation for 10min. @ 80C. The material was loaded on the gel and run for 1h @ 60w. The gel was transferred to a plastic support, wrapped, placed on film, exosed, and developed. The gel was placed on the developed film. A gel slice corresponding to the material of interest were cut from the gel by comparing with the film. The exercised gel was distributed in aliquots to filter columns. 500µL 500mM NH4Ac + 1mM EDTA pH 7.4 was added to each tube, incubate on heated shaker @ 65°C for 16 h. The material was recovered by centrifugation for 2min @1000 x RCF.

P4) Purification using HPLC

Purification was done using a Reverse Phase HPLC with a Waters XterraRP 8 column. A binary mobile phase gradient profile was used to elute the product using a 50 mM aqueous triethylammonium acetate buffer at pH 7.5 and 99%acetontrile/1% water solution. The purified material was concentrated by lyophilization and the resulting residue was dissolved in 5 mL of water.

P5) Purification by ion-exchange chromatography

The material was applied to a DEAE (Diethyl aminoethyl) column which had been washed 2 times with 10 mM Aq. AcOH. The material on DEAE was washed extensively with water. The material was then released from DEAE by adding 200 µl Release solution (1.5 M NaCl) and incubating at 25°C for 10 minutes in an eppendorph thermoshaker at 600 rpm. Water was added to the material to a final NaCl concentration of 0.5 M.

General procedures containing a quenching step:

Q1) Desphosphorylation to remove 5' phosphates from tags rendering them unable to participate in a tagging step, e.g. a ligation

The sample was dephosphorylated by first adding 80 µl SAP buffer (200 mM Hepes pH 7.8, 100 mM MgCl2) and 2 µl Shrimp Alkaline Phosphatase (USB, 40 U/µl) to the sample followed by incubation of the sample at 37°C for 1 hour. The phosphatase was inactivated by incubation at 68°C for 10 minutes. The sample was precipitated using 0.05 volumes of 5 M NaCl and 50% isopropanol and washed with cold 70% ethanol. A sample of the material was analysed by polyacrylamide gel electrophoresis and autoradiography to verify the efficiency of dephosphorylation.

General procedures containing a tagging step:

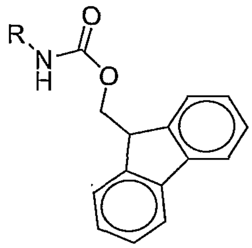
T1) 10 µl buffer containing 120 mM HEPES (2-[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-ethanesulfonic acid) pH 7.8, 40 mM $MgCl_2$, 40 mM DTT (dithiothretiol) and 4 mM ATP was added to each well. 500 pmol double-stranded tags (e.g., the combination A-0001 and Ax-0001) was also added. Annealing was then performed by a 80°C to 20° ramp in a thermocycler (Eppendorf Mastercycler Gradient). 1 µl of T4 DNA ligase (20 U/µl) was added to each well. Samples were then incubated in a PCR-machine with the following temperature profile: 25°C for 10 min, 45°C for 10 min, and 25°C for 10 min. The ligase was inactivated by incubating samples at 68°C for 10 min.

General procedures containing a deprotection step:

D1) Remove Fmoc protection groups on a DEAE ion exchange column releasing an amine

This procedure can also be used for removal of msec protection groups

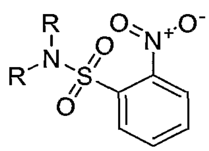
Fmoc (fluorenylmethoxycarbonyl) protection group:



To remove the Fmoc protection group, the material was applied to a DEAE (Diethyl aminoethyl) column which had been washed 2 times with 10 mM Aq. AcOH. The material on DEAE was washed with water and 2mL 10% Piperidine in dH2O was added folling by incubation for 10min at RT. A further 2mL 10% Pireridine in dH2O was added and incubated for 10min @ RT. The column was drained and washed with 4x10ml dH2O. The material was eluted by adding 750µL Release Solution (1.5M NaCl). Incubate @ 60C on shaker. Optionally repeat elution/release step.

D2) Remove Ns protection groups in organic solvent on a DEAE ion exchange column

Ns (2-Nitro-benzenesulfonyl) protection group:



To remove the Ns protection group, the material was applied to a DEAE (Diethyl aminoethyl) column which had been washed 2 times with 10 mM Aq. AcOH. The material on DEAE was washed with water followed by washing with DMF (dimethyl formamide). Then the material on DEAE was incubated in a solution of 0.5M mercaptoethanol and 0.25 M DIPEA (N,N'-Diisopropylethylamine) in dimethyl formamide and incubated for 24 hours at 25°C in an eppendorph thermoshaker at 600 rpm. Then the material on DEAE was washed with 0.3M AcOH in DMF, then twice with DMF and then with water. The Ns-deprotected material was then released from DEAE by adding 70 µl Release solution (1.5 M NaCl) and incubating at 25°C for 10 minutes in an eppendorph thermoshaker at 600 rpm. Water was added to the material to a final NaCl concentration of 0.5 M. Then the material was precipitated by adding one volume of isopropanol as described.

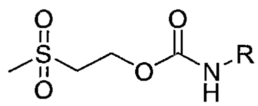
D3) Remove Fmoc protection groups in aqueous solution

This procedure can also be used for removal of msec protection groups in aqueous solution

Samples were redissolved in water and adjusted to 6% piperidine. Samples were then incubated at 25°C for 30 minutes to remove Fmoc protection groups.

D4) Remove Msec protection groups in aqueous solution

Msec (2-(methyl sulfonyl) ethyl carbamate) protection group used for protection of primary amines:

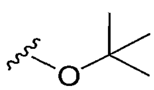


Msec protection groups were removed by dissolving the material in 25 µl 0.1 M Sodium Borate Buffer pH 10 and incubating at 40°C for 3 hours. Then the material was lyophilized and dissolved in 85 µl H_2O.

D5) Remove tBu, Me, and Et protection groups releasing the carboxylic acid in aqueous solution

The lyophilized material was dissolved in 20 µL 100 mM LiOH and incubated at 80 °C in PCR machine for 30 minutes. 40 µL 100 mM NaOAc buffer pH 5 was added

tBu protection group:

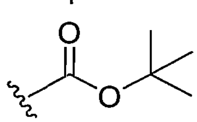


D6) Remove Boc protection group releasing the amine in aqueous solution

The lyophilized material was dissolved in 20 µL 37.5 mM NaOAc and 5 µL 1 M MgCl2

and incubated at 70 °C ON (Lid 100 °C) in PCR-machine

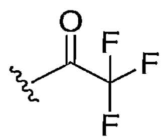
Boc protection group:



D6) Remove TFAc protection group releasing the amine in aqueous solution

The lyophilized material was dissolved in 20 µl and incubated at 45 °C ON (Lid 50°C) in PCR-machine for 18 hours.

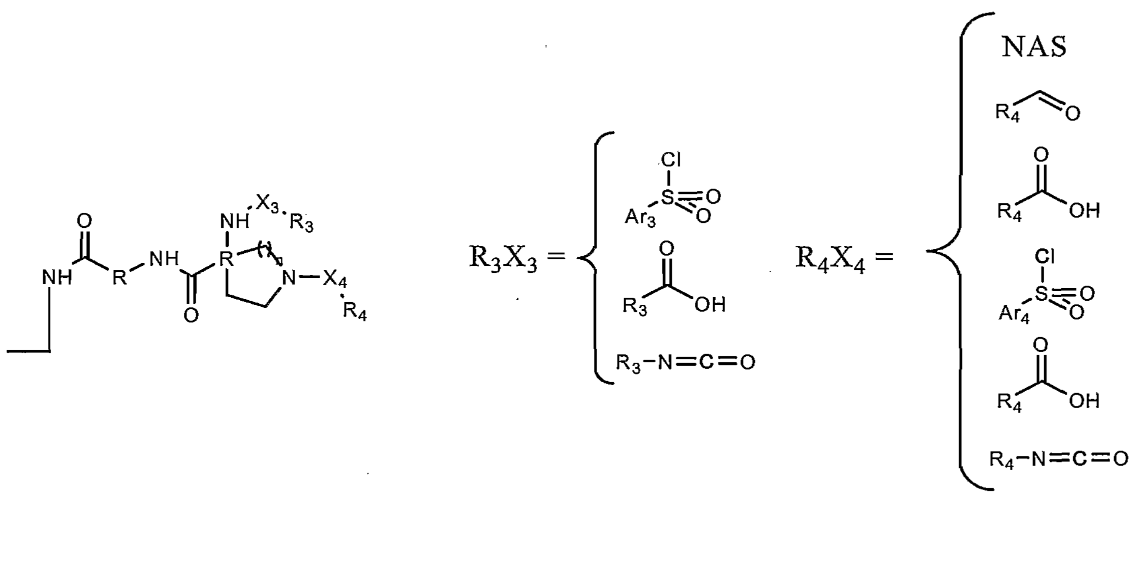
TFAc protection group:



Example 1: Synthesis and affinity selection of a library encoding on the order of 65.000 scaffolded compounds

This example illustrates the use of general procedures in the following order:
Position A building blocks (reactants) and tags: R1-P1-T1-P1-Q1-V2,
Position B building blocks (reactants) and tags: T1-P1-R1-P1-Q1-D4-V1,
Position C building blocks (reactants) and tags: T1-P1-(R1/R3/R2)-P1-Q1-V2-D2-V2,
Position D building blocks (reactants) and tags: T1-P1-(R1/R2/R3/R4/R5)-P1-D3-V2-P3

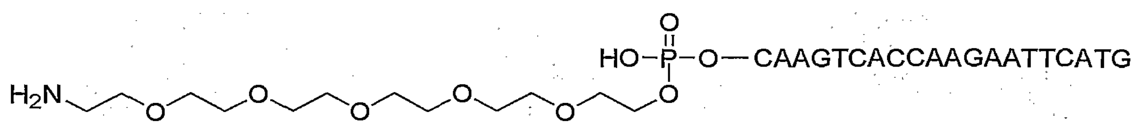
A library on the order of 65.000 DNA-tagged small molecules was synthesized. The synthesized small molecules were scaffolded (branched).



Scheme 1.1. Layout of the synthesized display molecules. R_3X_3 building blocks (reactants) included sulfonyl chlorides (Ar_3-SO_2-Cl), acids (R_3-COOH), and isocyanates (R_3-N=C=O). R_4X_4 building blocks (reactants) included chloro- and flouro-substituted heteroaromates (HetAr-Cl/F), aldehydes (R_4-C=O), acids (R_4-COOH),

sulfonyl chlorides (Ar_3-SO_2-Cl), and isocyanates (R_3-N=C=O)

The first set of building blocks (reactants) (see table 1.5A) were loaded onto a display oligo:



Scheme 1.2. The display oligo containing a chemical reaction site (H_2N), a polyethylenglycol linker, and an oligonucleotide tag.

Subsequently, Fmoc protection groups present on the loaded building blocks (reactants) was removed by incubating them in a solution of 6% piperidine in water at 25°C for 30 minutes. Samples were then purified using P-6 gel filtration spin columns (Biorad).

900 pmol Display oligo was added to each of 16 wells. In each well the display oligo carried a specific building block (position A building block).

Ligation of A-tags

10 µl buffer containing 120 mM HEPES (2-[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-ethanesulfonic acid) pH 7.8, 40 mM $MgCl_2$, 40 mM DTT (dithiothretiol) and 4 mM ATP was added to each well. 500 pmol double-stranded A-codons (e.g., the combination A-0001 and Ax-0001) was also added (See table 1.4A for tags and corresponding building blocks (reactants)). Annealing was then performed by a 80°C to 20° ramp in a thermocycler (Eppendorf Mastercycler Gradient) In one well 50 pmol double-stranded 5' phosphate 32-labeled A-codon was added. 1 µl of T4 DNA ligase (20 U/µl) was added to each well. Samples were then incubated in a PCR-machine with the following temperature profile: 25°C for 10 min, 45°C for 10 min, and 25°C for 10 min. The ligase was inactivated by incubating samples at 68°C for 10 min. 25 ul of water was then added to each sample. To allow verification of the efficiency of the following dephosphorylation step, a "Dummy A"

codon labelled with 5' phosphorus-32 was added to a sample. Bifunctional complexes were purified using gel-filtration with Bio-Gel P-6, (Bio-Rad) and the contents of the wells were pooled.

Desphosphorylation

The pooled sample was dephosphorylated by first adding 80 µl SAP buffer (200 mM Hepes pH 7.8, 100 mM MgCl2) and 2 µl Shrimp Alkaline Phosphatase (USB, 40 U/µl) to the pooled sample followed by incubation of the sample at 37°C for 1 hour. The phosphatase was inactivated by incubation at 68°C for 10 minutes. The sample was precipitated using 0.05 volumes of 5 M NaCl and 50% isopropanol and washed with cold 70% ethanol. A sample of the material was analysed by polyacrylamide gel electrophoresis and autoradiography to verify the efficiency of dephosphorylation.

Ligation of B-tags

The sample was dissolved in water and distributed equally to 16 wells. To each well 750 pmol double-stranded B-codon was added and ligation and dephosphorylation was performed as described for the ligation of A-codons. After ligation and inactivation of the enzyme, the samples were lyophilized.

Load of position B building blocks (reactants)

Each sample was dissolved 5 µl 200 mM Na-phosphate buffer pH 8.0 or 100 mM Na-Borate pH 9.0 or 100 mM Na-Borate pH 10.0 according to previously identified reaction conditions. To each well was added add 4 µl solution of a building block (100 mM in dimethyl sulfoxide). For each well 0.72 µl 0.5M DMT-MM solution in water was mixed with 0.28 µl 200 mM Na-phosphate buffer pH 8 and added to the well. The wells were then incubated at 30° C for 16 hours in a PCR-machine (Eppendorf Mastercycler Gradient). Then, 40 µl of water was added to each sample. Samples were purified using gel-filtration with Bio-Gel P-6, (Bio-Rad). The samples were pooled and purified by isopropanol precipitation as described.

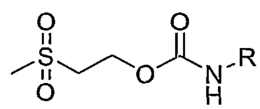
Desphosphorylation

The pooled sample was dephosphorylated by first adding 80 µl buffer containing 200 mM HEPES pH 7.8 and 100 mM $MgCl_2$ and 2 µl Shrimp Alkaline Phosphatase (USB, 40 U/µl) to the pooled sample followed by incubation of the sample at 37°C for 1 hour. The phosphatase was inactivated by incubation at 68°C for 10 minutes.

The sample was precipitated using 0.05 volumes of 5 M NaCl and 50% isopropanol and washed with cold 70% ethanol. A sample of the material was analysed by polyacrylamide gel electrophoresis and autoradiography to verify the efficiency of dephosphorylation.

Msec deprotection

Primary amines of position B building blocks (reactants) were protected by Msec groups:



Scheme 1.3 Msec (2-(methyl sulfonyl) ethyl carbamate) protection group used for protection of primary amines.

Msec protection groups were removed by dissolving the material in 25 µl 0.1 M Sodium Borate Buffer pH 10 and incubating at 40°C for 3 hours. Then the material was lyophilized and dissolved in 85 µl H_2O.

Ligation of C-tags

In each well ligation of double-stranded C-codons were performed as described for A- and B-codons.

Load of position C building blocks (reactants)

Samples to undergo isocyanate addition were redissolved in 8 µl buffer (100mM sodium borate and 100mM sodium phosphate pH 8.0). 1 µl of a specific building block (300 mM in CH_3CN) was added to each well and incubated at 50ºC for 16 hours. Then, 40 µL of water was added to each sample.

Samples to undergo sulfonylation were dissolved in 8 µl 100 mM Sodium Borate buffer pH 9. Then 2 µl specific building block (100 mM in tetrahydrofuran) was then to each well and incubated at 30°C for 16 hours. Then, 40 µl of water was added to each sample.

Samples to undergo acylation were dissolved in 5 µl 200 mM Na-phosphate buffer pH 8.0 or 100 mM Na-Borate pH 9.0 or 100 mM Na-Borate pH 10.0. Then, 4 µl specific building block (100 mM in dimethylsulfoxide) was added to each well. Then

1 µl DMT-MM mix (0.36 M DMT-MM in water and 56 mM Na-phosphate buffer pH 8) was mixed in each well and the sample was incubate at 30° C for 16 hours. Then, 40 µl water was added to each sample.

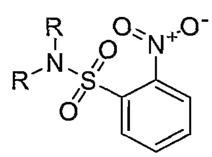
Samples were purified by gel-filtration as described.

Desphosphorylation

The pooled sample was dephosphorylated by first adding 80 µl buffer (200 mM Hepes pH 7.8, 100 mM MgCl2) and 2 µl Shrimp Alkaline Phosphatase (USB, 40 U/µl) to the pooled sample followed by incubation of the sample at 37°C for 1 hour. The phosphatase was inactivated by incubation at 68°C for 10 minutes. The sample was precipitated using 0.05 volumes of 5 M NaCl and 50% isopropanol and washed with cold 70% ethanol. A sample of the material was analysed by polyacrylamide gel electrophoresis and autoradiography to verify the efficiency of dephosphorylation.

Ns protection group removal

Secondary amines of position B building blocks (reactants) were protected using Ns:



Scheme 1.4 Ns (2-Nitro-benzenesulfonyl) protection group used for protection of seconday amines.

To remove the Ns protection group, the material was applied to a DEAE (Diethyl aminoethyl) column which had been washed 2 times with 10 mM Aq. AcOH. The material on DEAE was washed with water followed by washing with DMF (dimethyl formamide). Then the material on DEAE was incubated in a solution of 0.5M mercaptoethanol and 0.25 M DIPEA (N,N'-Diisopropylethylamine) in dimethyl formamide and incubated for 24 hours at 25°C in an eppendorph thermoshaker at 600 rpm. Then the material on DEAE was washed with 0.3M AcOH in DMF, then twice with DMF and then with water. The Ns-deprotected material was then released from DEAE by adding 70 µl Release solution (1.5 M NaCl) and incubating at 25°C

for 10 minutes in an eppendorph thermoshaker at 600 rpm. Water was added to the material to a final NaCl concentration of 0.5 M. Then the material was precipitated by adding one volume of isopropanol as described.

Ligation of D-tags

D-tags were ligated as described. Then samples were purified using gel-filtration as described and lyophilized.

Load of position D building blocks (reactants)

Samples to undergo isocyanate addition were redissolved in 8 µl buffer (100mM sodium borate and 100mM sodium phosphate pH 8.0) 1 µl of a specific building block (300 mM in CH_3CN) was added to each well and incubated at 50°C for 16 hours. Then, 40 µL of water was added to each sample.

Samples to undergo sulfonylation were dissolved in 8 µl 100 mM Sodium Borate buffer pH 9. 2 µl specific building block (100 mM in tetrahydrofuran) was then to each well and incubated at 30°C for 16 hours. Then, 40 µl of water was added to each sample.

Samples to undergo acylation were dissolved in 5 µl 200 mM Na-phosphate buffer pH 8.0 or 100 mM Na-Borate pH 9.0 or 100 mM Na-Borate pH 10.0. Then, 4 µl specific building block (100 mM in dimethylsulfoxide) was added to each well. Then 1 µl DMT-MM mix (0.36 M DMT-MM in water and 56 mM Na-phosphate buffer pH 8) was mixed in each well and the sample was incubate at 30° C for 16 hours. Then, 40 µl water was added to each sample.

Samples to undergo reductive amination were dissolved in 15 µl 200 mM NaOAc buffer pH 5.0 5 ul specific BB was added to each well (200 mM in DMSO) and incubate at 30°C for 1 h. Then 5 µl of freshly prepared 140 mM NaCNBH3 (REA000025; 8.8 mg/ml) in NaOAc buffer pH 5.0 to was added each well and the samples were incubated at 30°C for 16 hours in a PCR-machine. Then 25 µl water was added to each sample.

Samples to undergo nucleophilic aromatic substitution were dissolved in 12 µl 100 mM Borate Buffer pH 9. Then 12 µl specific BB was added to each well (100 mM in

DMSO) and all wells were incubated for 16 hours at 90°C. Then, 40 µl water was added to each sample.

Samples were then purified by gel-filtration as described.

Fmoc deprotection

Samples were redissolved in water and adjusted to 6% piperidine. Samples were then incubated at 25°C for 30 minutes to remove Fmoc protection groups. Samples were then again precipitated using isopropanol.

The combined material was redissolved in water and adjusted with polyacrylamide gel electrophoresis loading buffer . The material was electrophoresed and purified by isolating the material corresponding to bifunctional complexes with 4 tags. The single stranded bifunctional complexes were eluted from the gel, precipitated using isopropanol as described, and purified by gel-filtration as described.

Affinity selection

Prior to selection the single stranded bifunctional complexes were converted to double-stranded for by extending a primer containing a sequence informative of the selection using the single-stranded tag of the bifunctional comples as a template. 200 pmol primer (5'- AAGGAACATCATCATGGAT) was mixed with 20 pmol bifunctional complexes and lyophilized. The sample was redissolved in 2.5 reaction buffer and 5 µl each dNTP (25 mM stock concentration) was added. The mixture was heated to 80°C and slowly cooled to 55°C. Then 2.5 µl Taq Polymerase (5 units / µl) was added and the extension reaction was allowed to proceed for 1 hour. Then 25 µl water was added and the sample was purified using gel-filtration and used for affinity selection.

A fraction of the obtained bifunctional complexes was lyophilized and dissolved in 5 µl thrombin buffer (137 mM NaCl, 2.7 mM KCl, 10 mM sodium phosphate, 0,1% PEG8000). 50 µl streptavidin sepharose (Amersham Biosciences) slurry was washed in 4x 100 µl thrombin buffer and resuspended in 50 µl thrombin buffer. Then 2 units biotinylated thrombin (Novagen) was added to the streptavidin sepharose slurry and the slurry was incubated at 15°C with agitation (1400 rpm) for 30 minutes and subsequently washed 4 times with 100 µl thrombin buffer. A 10 µl Eppendorf tip was packed with glass wool up to the 2.5 µl mark. The streptavidin sepharose was

applied to the tip and washed 3 times with 100 µl thrombin buffer by applying vacuum to the bottom end of the tip. The library was applied to the column and allowed to soak in. Then the column was washed 5 times with 100 µl thrombin buffer. Bifunctional complexes were eluted by applying 25 µl of a nanomolar ligand (100 µM in PBS) to the column for 10 min followed by centrifugation of the column (1000 rcf for 30 seconds). An additional 25 µl PBS was applied to the column and spun through. The eluted material was re-applied to a fresh column. This cycle was repeated 4 times. A 10 µl sample of eluted material was used PCR using the forward and reverse primers 5'-CAAGTCACCAAGAATTCATG and 5'-AAGGAACATCATCATGGAT. The PCR product was cloned and sequenced using standard methods.

Table 1.1 Layout of tags (A, B, C, and D) and anti-tags (Ax, Bx, Cx, Dx) showing codons (XXXXXXXXXXXXXXXXXXXX). The specific nucleotide sequences of overhang sequences are shown.

A XXXXXXXXXXXXXXXXXXXXCCTAGGACCA
B XXXXXXXXXXXXXXXXXXXXGTGTCACTTA
C XXXXXXXXXXXXXXXXXXXXGTGCACGTGT
D XXXXXXXXXXXXXXXXXXXXGAATTCTACTCTCCTCAAGGTGATCCATGATGATGTTCCTT
Ax XXXXXXXXXXXXXXXXXXXXCATGAATTCTTGGTGACTTG
Bx XXXXXXXXXXXXXXXXXXXXTGGTCCTAGG
Cx XXXXXXXXXXXXXXXXXXXXTAAGTGACAC
Dx XXXXXXXXXXXXXXXXXXXXACACGTGCAC

Table 1.2 Examples of specific tags and antitags. Both codon and overhang sequences are shown.

Tag	Sequence
A-0001	pTGTTGTCCATGATGCTTCCTCCTAGGACCA
A-0002	pCAACTTGATCTCCAGTCGTCCCTAGGACCA
B-0001	pCTAGTGGTCGAAGTTGCACAGTGTCACTTA
B-0002	pCCTACGTCTTCATGGACCTTGTGTCACTTA
C-0001	pTTCGTCCATGCACATGATCTGTGCACGTGT
C-0002	pCAGTTCCTCCAAGCAGTAGGGTGCACGTGT
D-0001	pGTTCATCGTCTTCTAGGTGCGAATTCTACTCTCCTCAAGGTGATCCATGATGATGTTCCTT
D-0002	pTGAGGTTCGAGGTTGACGATGAATTCTACTCTCCTCAAGGTGATCCATGATGATGTTCCTT
Ax-0001	AGGAAGCATCATGGACAACACATGAATTCTTGGTGACTTG
Ax-0002	GACGACTGGAGATCAAGTTGCATGAATTCTTGGTGACTTG
Bx-0001	TGTGCAACTTCGACCACTAGTGGTCCTAGG
Bx-0002	AAGGTCCATGAAGACGTAGGTGGTCCTAGG
Cx-0001	AGATCATGTGCATGGACGAATAAGTGACAC
Cx-0002	CCTACTGCTTGGAGGAACTGTAAGTGACAC
Dx-0001	GCACCTAGAAGACGATGAACACACGTGCAC
Dx-0002	ATCGTCAACCTCGAACCTCAACACGTGCAC

“p” denotes a 5’ phosphate

Table 1.4A Building blocks (reactants) used in synthesis position A and codons of the corresponding A-tags

BB A	Tag A codon
Blank	AGTGCTCACACGACTGCTCG
BBA000008	AGCTACGACAAGACTAGGAT
BBA000890	CGTCCACTACCATCGACGAC
BBA001092	CCAACTTGTAGGTGAGGACT
REA000251	CTGCTGTTGGACTGCTTGTA
REA000252	CTTCCAGGTCCTCGTAGTTC
REA000778	AACATGCTCTAGGTGTCGTC
REA001185	ACCTGCACCTGGATGGATCG
REA001315	AACGAGGTCAGACGAAGCAC
REA001763	CTCTCTAGTCCACAAGATGC
REA001764	ATCTCAAGTACGACACATCC
REA001766	CCATCACATCAGCAGGTAGA
REA001774	TGTGTTGTGCTTGACCATCC
REA001775	CAGACCTGTCTCCACGTAGC
REA001776	GCACTTGTCGATCAAGCAGA
REA001779	TGGTCCTTGCTTGATGGAGT
Dummy A	ATCGTACAGACTCCTCACAG

Table 1.4B Building blocks (reactants) used in synthesis position B and codons of the corresponding B-tags

BB B	Tag B codon
Blank	TCCAAGCACGTCTCGTACTC
REA001706	GGTCGACCAGATGGACACTT
REA001710	CATCATCTGTACAGGATGGT
REA001711	TTCCAACTGCAAGGTACAGG
REA001713	TAGCACCTACAAGATGGAGT
REA001714	CTCGACACCAGGTCCAGAAG
REA001720	GGTCATCTGAGCAACGTTGT
REA001732	CACAAGCTAGGTACATGGAC
REA001737	TGCAGCAGCTTGCTCGTACT
REA001738	GTCCATGTCCAAGCATGAAG
REA001739	TCCATCTCTAGGTTGCACAC

REA001740	ATGCTACACCACTGCTGTGC
REA001741	CAACATGGAGAGTGGAACAT
REA001742	ACTCCATCCACTTCACAGAG
REA001743	CTCCAGACTACCTGTGGACG
REA001744	CGAGCAAGACATGAGCACTC
Dummy B	CCTCGTCCTGATGTTGCATC

Table 1.4C Building blocks (reactants) used in synthesis position C and codons of the corresponding C-tags

BB C	**Tag C codon**
Blank	TCAGAACCATGCACTTGACG
REA001526	GGAACATGCTGGAAGACCAG
REA001527	TACAGACTGAGCTTCACTTG
REA001534	TCCTGATGGTGTACCACCTT
REA001535	AAGCAGCTCTGTCGAGCAAT
REA001537	ATCAACCAAGGACATCTCTG
REA000032	CCTTGTAGGTCGTAGTGCAT
REA001467	ACCTTCACGATCAGAGCTAT
REA001469	GATGTTGAGGACGTAGTGTG
REA001471	CTTCGTCGAAGACTGAGTCA
REA001475	ACGACTGTCGTACGAGACGT
BBA000820	CGATCTGGTTGACGAACAGC
BBA000828	CCACGATCTTGAGTGTACGG
BBA000836	CACTGAGCAGCTTCTTCCAT
REA000736	CTCTTGGTTCCTAGGAGACA
REA001712	GTCAGGACAACTCAGTGCAG
Dummy C	CGTGCTACCACACTCACAAT

Table 1.4D Building blocks (reactants) used in synthesis position D and codons of the corresponding D-tags

BB D	**Tag D codon**
Blank	TCACATGACCAGCACGTGCG
REA001526	CGATCAAGCTACAGAAGAAG
REA001527	TGGACTCTGTCGAAGGTACA
REA001535	CTGTAGCATCCACTCCATCC

REA000032	GACTGTGGTGACACCTGACT
REA001467	GCTTCGACAGACATCACTCG
REA001469	ATGGACAGTGGACACTCATT
BBA000031	GCTTCTCCTGGTTGATGGTC
REA000736	CGTCGATGGACGTGTCGATT
REA002313	CGTTCCAACCAACCTTGGAG
REA000457	CGAACAGAACTAGCACGTCA
REA001223	GAAGTTCCTCTGGTCTAGGG
REA001366	GGTCTAGTAGCATGATCGAA
REA001263	CTTCTTGGAACCTGAGCTTA
REA001516	TTGCTCAGCATCCTTGAACT
REA001754	TGTTCCTGGTACACGAGGAG

Table 1.5A Position A building blocks (reactants). The unprotected structures are shown. The primary amines were protected by Fmoc groups during loading. After loading the Fmoc groups were removed.

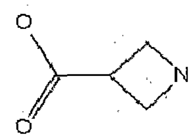
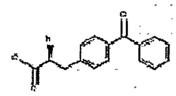
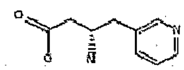
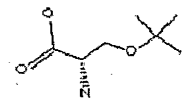
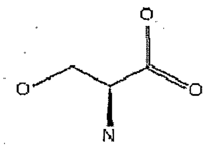
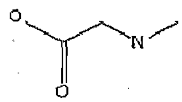
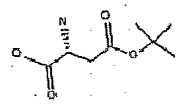
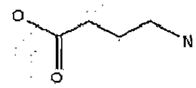
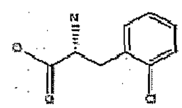
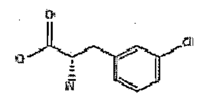
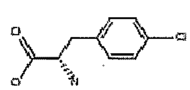
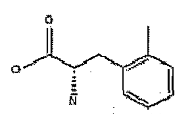
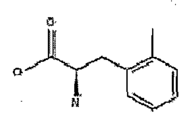
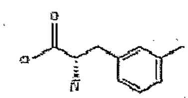
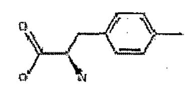
BBA000008 	BBA000890 	BBA001092 	REA000251 	REA000252 
REA000778 	REA001185 	REA001315 	REA001763 	REA001764 
REA001766 	REA001774 	REA001775 	REA001776 	REA001779 

Table 1.5B Position B building blocks (reactants). The unprotected structures are shown. The primary amines were protected by Msec groups and secondary amines were protected by Ns during loading. After loading the protection groups were removed sequentially.

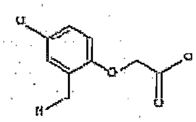
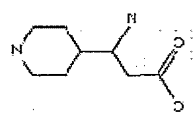
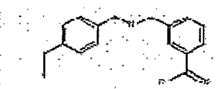
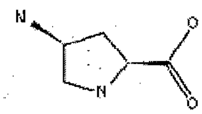
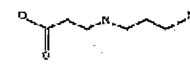
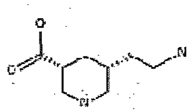
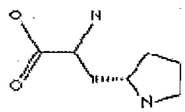
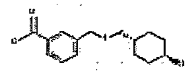
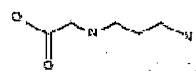
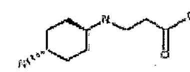
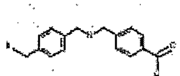
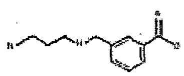
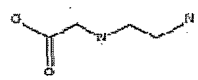
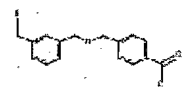
REA001710 	REA001706 	REA001711 	REA001713 	REA001714 
REA001720 	REA001732 	REA001737 	REA001738 	REA001739 
REA001740 	REA001741 	REA001742 	REA001743 	REA001744 

Table 1.5C Position C building blocks (reactants).

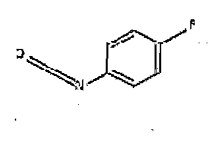
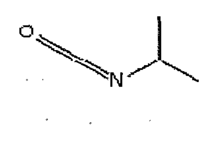
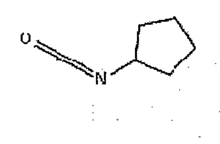
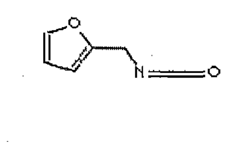
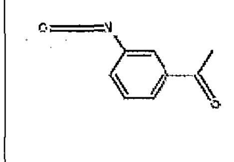
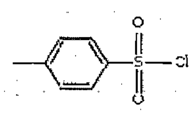
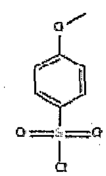
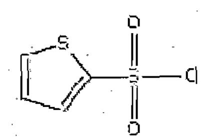
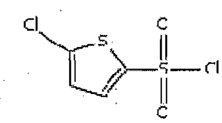
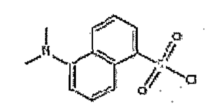
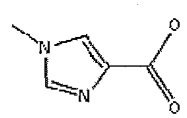
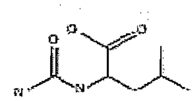
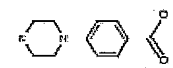
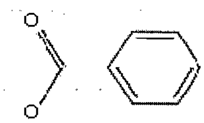
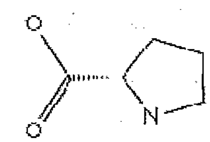
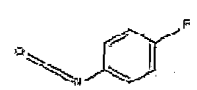
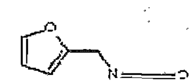
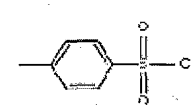
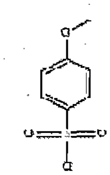
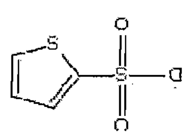
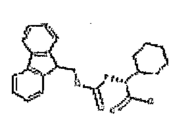
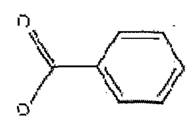
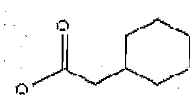
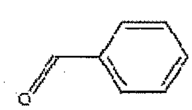
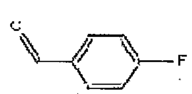
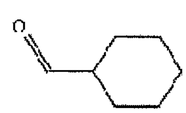
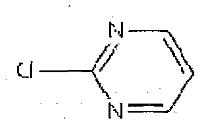
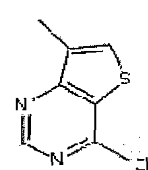
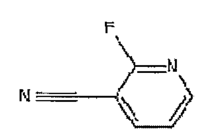
REA001526 	REA001527 	REA001534 	REA001535 	REA001537 
REA000032 	REA001467 	REA001469 	REA001471 	REA001475 
BBA000820 	BBA000828 	BBA000836 	REA000736 	REA001712 

Table 1.5D Position D building blocks (reactants).

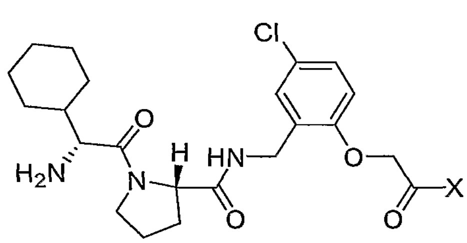
REA001526 	REA001527 	REA001535 	REA000032 	REA001467 
REA001469 	BBA000031 	REA000736 	REA002313 	REA000457 
REA001223 	REA001356 	REA001263 	REA001516 	REA001754 

Selection results

Table 1.6. Selection output sample showing the number of observations (n) of each combination of codons A, B, C, and D.

	Position			
n	A	B	C	D
2	BBA001092	REA001710	BBA000820	BBA000031
3	REA001764	REA001710	REA001526	BBA000031
1	REA001315	REA001710	REA001537	BBA000031
6	BBA000890	REA001710	REA001712	BBA000031
4	REA001774	REA001710	REA001712	BBA000031
3	REA000252	REA001710	REA001712	BBA000031
2	REA000251	REA001710	REA001712	BBA000031
1	REA001775	REA001710	REA001712	BBA000031
1	REA001764	REA001710	REA001712	BBA000031
2	BBA000890	REA001710	REA001712	REA001535
4	REA001185	REA001720	REA001471	BBA000031
3	REA001766	REA001732	REA001526	REA001535
1	REA001766	REA001732	REA001527	REA001527
1	REA001766	REA001732	REA001527	REA001535

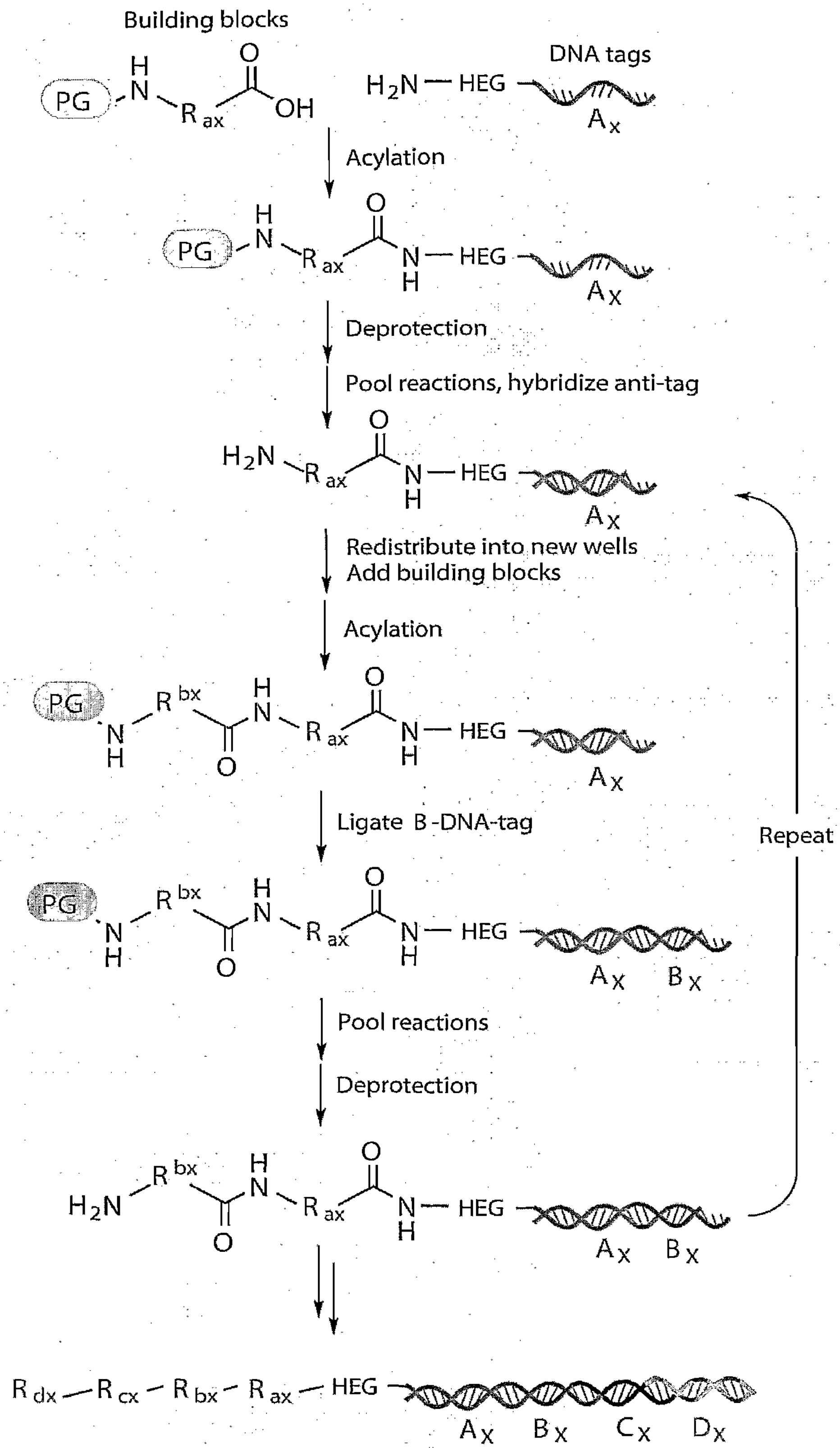
The building block combination X-REA001710-REA001712-BBA000031 (X can be different position A building blocks (reactants)) corresponds to ligands with Ki values against human thrombin in the low nanomolar to subnanomolar range (Tucker TJ et al. *J. Med. Chem.* **1998,** *41,* 3210-3219):



Scheme 1.5 Chemical structure corresponding to the building block combination X-REA001710-REA001712-BBA000031

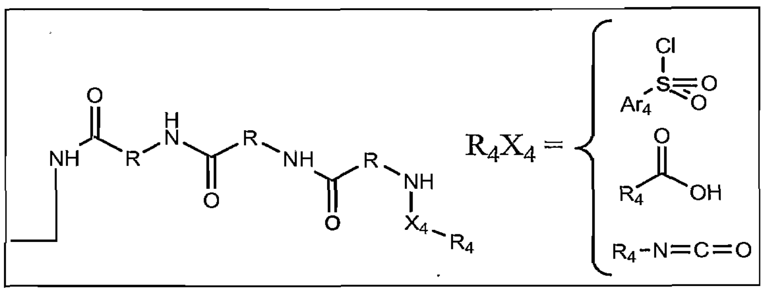
Example 2 : Synthesis and affinity selection of a library encoding on the order of 85.000.000 compounds

A library encoding approximately 85.000.000 compounds was generated using 4 rounds of building block addition.



Building blocks
PG
H
N
R ax
O
OH
H2N — HEG
DNA tags
Ax
Acylation
Deprotection
Pool reactions, hybridize anti-tag
Redistribute into new wells
Add building blocks
Acylation
R bx
Ligate B-DNA-tag
Bx
Pool reactions
Deprotection
Repeat
R dx — R cx — R bx — R ax — HEG
Cx
Dx

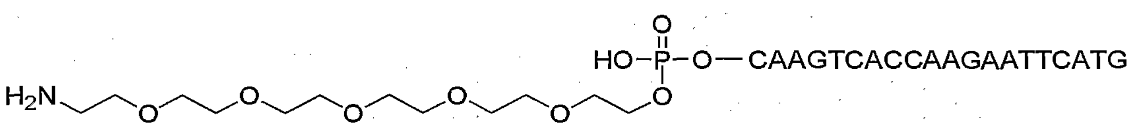
Scheme 2.1 (a) Synthesis of small molecules composed of 4 building blocks (reactants) and encoded by 4 tags. The process is detailed in the text.



Scheme 2.2 Layout of the synthesized display molecules. R_4X_4 building blocks (reactants) included acids (R_4-COOH), sulfonyl chlorides (Ar_4-SO_2-Cl), and isocyanates (R_4-N=C=O)

The first set of building blocks (reactants) were loaded onto a display oligo:

Display Oligo



Scheme 2.3 The display oligo containing a chemical reaction site (H_2N), a polyethylenglycol linker, and an oligonucleotide tag.

Subsequently, Fmoc protection groups present on the loaded building blocks (reactants) was removed by incubating them in a solution of 6% piperidine in water at 25°C for 30 minutes. Samples were then purified using P-6 gel filtration spin columns (Biorad).

900 pmol Display oligo was added to each of 96 wells. In each well the display oligo carried a specific building block (position A building block).

Ligation of A-tags

10 ul buffer (120 mM Hepes pH 7.8, 40 mM MgCl2, 40 mM DTT and 4 mM ATP) was added to each well. 500 pmol double-stranded A-codons (e.g., the combination A-0001 and Ax-0001) was also added. Annealing was then performed by a 80°C to 20° ramp in a PCR machine (Eppendorf Mastercycler Gradient) In one well 50 pmol double-stranded 5' phosphate 32-labeled A-codon was added. 1 µl of T4 DNA ligase (20 U/µl) was added to each well. Samples were then incubated in a PCR-machine with the following temperature profile: 25°C for 10 min, 45°C for 10 min, and 25°C for 10 min. The ligase was inactivated by incubating samples at 68°C for 10 min. 25 ul of water was then added to each sample. To allow verification of the efficiency of the following dephosphorylation step, a "Dummy A" codon labelled with 5' phosphor-32 was added to a sample. Bifunctional complexes were purified using gel-filtration with Bio-Gel P-6, (Bio-Rad) and pooled.

Desphosphorylation

The pooled sample was dephosphorylated by first adding 92 µl SAP buffer (200 mM Hepes pH 7.8, 100 mM MgCl2) and 4 µl Shrimp Alkaline Phosphatase (USB, 40 U/µl) to the pooled sample followed by incubation of the sample at 37°C for 1 hour. The phosphatase was inactivated by incubation at 68°C for 10 minutes. The sample was precipitated using 0.05 volumes of 5 M NaCl and 50% isopropanol and washed with cold 70% ethanol. A sample of the material was analysed by polyacrylamide gel electrophoresis and autoradiography to verify the efficiency of dephosphorylation.

Ligation of B-tags

The sample was dissolved in water and distributed equally to 96 wells. To each well 750 pmol double-stranded B-codon was added and ligation and dephosphorylation was performed as described for the ligation of A-codons. After ligation and inactivation of the enzyme, the samples were lyophilized.

Load of position B building blocks (reactants)

Each sample was dissolved 5 µl 200 mM Na-phosphate buffer pH 8.0 or 100 mM Na-Borate pH 9.0 or 100 mM Na-Borate pH 10.0 according to previously identified reaction conditions. To each well was added add 4 µl solution of a building block

(100 mM in dimethyl sulfoxide). For each well 0.72 µl 0.5M DMT-MM solution in water was mixed with 0.28 µl 200 mM Na-phosphate buffer pH 8 and added to the well. The wells were then incubated at 30° C for 16 hours in a PCR-machine (Eppendorf Mastercycler Gradient). Then, 40 µl of water was added to each sample. Samples were purified using gel-filtration with Bio-Gel P-6, (Bio-Rad). The samples were pooled and purified by isopropanol precipitation as described.

Fmoc deprotection

Samples were redissolved in water and adjusted to 6% piperidine. Samples were then incubated at 25°C for 30 minutes to remove Fmoc protection groups. Samples were then again precipitated using isopropanol. The samples were redissolved in water and distributed equally to 96 wells.

Ligation of C-tags

In each well ligation of double-stranded C-codons were performed as described for A- and B-codons.

Load of position C building blocks (reactants)

Position C building blocks (reactants) were loaded as described for position B building blocks (reactants). Following loading, the samples were gel-filtration purified, desphosphorylated, precipitated using isopropanol and Fmoc protection groups were removed as described.

Ligation of D-tags

D-codons were ligated as described. Then samples were purified using gel-filtration as described and lyophilized.

Load of position D building blocks (reactants)

Samples to undergo isocyanate addition were redissolved in 8 µl buffer (100mM sodium borate and 100mM sodium phosphate pH 8.0) 1 µl of a specific building block (300 mM in CH_3CN) was added to each well and incubated at 50°C for 16 hours in a in PCR-machine (Eppendorf Mastercycler Gradient). Then, 40 µL of water was added to each sample.

Samples to undergo sulfonylation were dissolved in 8 µl 100 mM Sodium Borate buffer pH 9. 2 µl specific building block (100 mM in tetrahydrofuran) was then to

each well and incubated at 30°C for 16 hours in a PCR-machine. Then, 40 µl of water was added to each sample.

Samples to undergo acylation were dissolved in 5 µl 200 mM Na-phosphate buffer pH 8.0 or 100 mM Na-Borate pH 9.0 or 100 mM Na-Borate pH 10.0. Then, 4 µl specific building block (100 mM in dimethylsulfoxide) was added to each well. Then 1 µl DMT-MM mix (0.36 M DMT-MM in water and 56 mM Na-phosphate buffer pH 8) was mixed in each well and the sample was incubate at 30° C for 16 hours in a PCR-machine. Then, 40 µl water was added to each sample.

Samples were purified by gel-filtration as described.

Fmoc deprotection

Samples were redissolved in water and adjusted to 6% piperidine. Samples were then incubated at 25°C for 30 minutes to remove Fmoc protection groups. Samples were then again precipitated using isopropanol.

The combined material was redissolved in water and adjusted with polyacrylamide gel electrophoresis loading buffer. The material was electrophoresed and purified by isolating the material corresponding to bifunctional complexes with 4 tags. The single stranded bifunctional complexes were eluted from the gel, precipitated using isopropanol as described, and purified by gel-filtration as described.

Prior to selection the single stranded bifunctional complexes were converted to double-stranded for by extending a primer containing a sequence informative of the selection using the single-stranded tag of the bifunctional complexes as a template. 200 pmol primer (5'-TCTGGTGGTCTACGTGCTCTAAGGAACATCATCATGGATC) was mixed with 20 pmol bifunctional complexes and lyophilized. The sample was redissolved in 2.5 reaction buffer and 5 µl each dNTP (25 mM stock concentration) was added. The mixture was heated to 80°C and slowly cooled to 55°C. Then 2.5 µl Taq Polymerase (5 units / µl) was added and the extension reaction was allowed to proceed for 1 hour. Then 25 µl of water was added and the sample was purified using gel-filtration and used for affinity selection.

Selection

A fraction of the obtained bifunctional complexes was lyophilized and dissolved in 5 µl thrombin buffer (137 mM NaCl, 2.7 mM KCl, 10 mM sodium phosphate, 0.1 % PEG8000). 50 µl streptavidin sepharose (Amersham Biosciences) slurry was washed in 4x 100 µl thrombin buffer and resuspended in 50 µl thrombin buffer. Then biotinylated thrombin (Novagen – 2 units) was added to the streptavidin sepharose slurry and the slurry was incubated at 15ºC with agitation (1400 rpm) for 30 minutes and subsequently washed 4 times with 100 µl thrombin buffer. A 10 µl Eppendorf tip was packed with glass wool up to the 2.5 µl mark. The streptavidin sepharose was applied to the tip and washed 3 times with 100 µl thrombin buffer by applying vacuum to the bottom end of the tip. The library was applied to the column and allowed to soak in. Then the column was washed 5 times with 100 µl thrombin buffer. Bifunctional complexes were eluted by applying 25 µl of a nanomolar ligand (100 µM in PBS) to the column for 10 min followed by centrifugation of the column (1000 rcf for 30 seconds). An additional 25 µl PBS was applied to the column and spun through. The eluted material was re-applied to a fresh column. This cycle was repeated 4 times. A 10 µl sample of eluted material was used PCR using the forward and reverse primers 5'-CAAGTCACCAAGAATTCATG and 5'-TCTGGTGGTCTACGTGCTCT. The PCR product was clones and sequenced using standard methods.

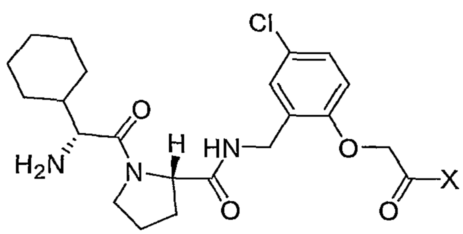
Selection results

Table 2.1 Selection output sample showing the number of observations (n) of each combination of codons A, B, C, and D.

	Position			
n	A	B	C	D
1	REA002420	REA001464	REA001829	REA002088
1	REA001821	REA001710	BBA001023	BBA000031
1	REA002407	REA001710	BBA001023	BBA000031
1	REA001423	REA001710	BBA001023	BBA000031
1	REA001828	REA001906	REA002449	REA002036
1	REA001416	REA001917	REA001557	REA000798
2	BBA000029	REA001936	REA002446	REA002067
1	REA002420	REA002411	REA001829	REA002088

1	REA001329	REA002438	BBA000029	REA002042

The building block combination X-REA001710-BBA001023-BBA000031 (X can be different position A building blocks (reactants)) corresponds to ligands with Ki values against human thrombin in the low nanomolar to subnanomolar range (Tucker TJ et al. *J. Med. Chem.* **1998,** *41,* 3210-3219):



Scheme 2.4 Chemical structure corresponding to the building block combination X-REA001710-BBA001023-BBA000031

Table 2.2 Layout of tags (A, B, C, and D) and anti-tags (Ax, Bx, Cx, Dx) showing codons (XXXXXXXXXXXXXXXXXXXX). The specific nucleotide sequences of overhang sequences are shown.

A	XXXXXXXXXXXXXXXXXXXXCCTAGGACCA
B	XXXXXXXXXXXXXXXXXXXXGTGTCACTTA
C	XXXXXXXXXXXXXXXXXXXXGTGCACGTGT
D	XXXXXXXXXXXXXXXXXXXXGAATTCTACTCTCCTCAAGGTGATCCATGATGATGTTCCTT
Ax	XXXXXXXXXXXXXXXXXXXXCATGAATTCTTGGTGACTTG
Bx	XXXXXXXXXXXXXXXXXXXXTGGTCCTAGG
Cx	XXXXXXXXXXXXXXXXXXXXTAAGTGACAC
Dx	XXXXXXXXXXXXXXXXXXXXACACGTGCAC

Table 2.3 Examples of specific tags and antitags. Both codon and overhang sequences are shown.

Tag	Sequence
A-0001	pTGTTGTCCATGATGCTTCCTCCTAGGACCA
A-0002	pCAACTTGATCTCCAGTCGTCCCTAGGACCA
B-0001	pCTAGTGGTCGAAGTTGCACAGTGTCACTTA
B-0002	pCCTACGTCTTCATGGACCTTGTGTCACTTA
C-0001	pTTCGTCCATGCACATGATCTGTGCACGTGT
C-0002	pCAGTTCCTCCAAGCAGTAGGGTGCACGTGT
D-0001	pGTTCATCGTCTTCTAGGTGCGAATTCTACTCTCCTCAAGGTGATCCATGATGATGTTCCTT
D-0002	pTGAGGTTCGAGGTTGACGATGAATTCTACTCTCCTCAAGGTGATCCATGATGATGTTCCTT
Ax-0001	AGGAAGCATCATGGACAACACATGAATTCTTGGTGACTTG
Ax-0002	GACGACTGGAGATCAAGTTGCATGAATTCTTGGTGACTTG
Bx-0001	TGTGCAACTTCGACCACTAGTGGTCCTAGG
Bx-0002	AAGGTCCATGAAGACGTAGGTGGTCCTAGG
Cx-0001	AGATCATGTGCATGGACGAATAAGTGACAC
Cx-0002	CCTACTGCTTGGAGGAACTGTAAGTGACAC

Dx-0001 GCACCTAGAAGACGATGAACACACGTGCAC

Dx-0002 ATCGTCAACCTCGAACCTCAACACGTGCAC

“p” denotes a 5’ phosphate

Table 2.4 Building blocks (reactants) and their corresponding tag codons used in the library synthesis.

BB A	Tag A codon
BBA000029	GTGCTACTGAGATGTTGCAG
BBA000890	GCTGATGAGTTCGAGTTCTA
REA000250	GGTAGCAAGATGGTACTACG
REA000778	CCACGACATCAACCATGGTG
REA001143	GATCACCTGTCGATGAACGA
REA001329	TCTACGTTCACAGATGCTCG
REA001398	TCATGGTCTGCACTCAGGAT
REA001399	CCTGTACCAACTGGACATCG
REA001403	TGCACTGTACGAGCAGGTCT
REA001405	TAGGTCAGGAGTACAACACT
REA001410	CTCGTTGTCCAACATCACAT
REA001411	CACACGATGCTGTAGCTCTA
REA001415	GAACTCTAGGTGGAAGGAAA
REA001416	TACTGCATGTACCACCATGA
REA001419	ACAGGAAGACGTGCATGTAC
Blank	TGGTCTCGTTCTCGTCACAG
REA001422	TACAGAAGCATCGAGTAGCT
REA001423	GGTCCTCTCAAGATGTGGAA
REA001424	GTGGTGAGCTTGTGGTCGAA
REA001425	CGAACCTCCAGTAGCATGGT
REA001426	CTCATCCACGAGGAGCAAGT
REA001446	ATCATGCAACCTACGAGCTT
REA001464	TTGGAGGTACGATCCACACA
REA001767	CTGCTTCGTACCACAAGCTC
REA001769	TCACCACTTCCAGATCGTTC
REA001773	CTCTTCAACCTGAGAACAAC
REA001774	TGTGGTGGTGCTCGTACTGC
REA001775	CGTTCCTCTCAGAACCAGAG
REA001780	TGGAAGCTACCATCTCGTGC
REA001781	GTGGATCGACCTCTAGCAAA
REA001782	CCAGTGCTAGGTTGCTCGAC
REA001785	CAAGTTCTTGCACTCGATCT

BB B	Tag B codon
Blank	TTCGAGCTACACCTGCTGAC
REA001290	GGTCCAGCAAGAGCACCATA
BBA001092	CTGGTCCTTCAGGAACGTAA
REA001291	TAGGTACCTGGTAGTGAAGT
REA001464	GGTTGTTCCTGCTTGCTCAG
REA001806	CCAGTGGACTGACCTTGTGC
REA002437	CGTGGTTCATGGAAGCAACG
REA002438	TCCTAGAGACATGCATGCAA
BBA000008	CGAGCTGGATGCTACACTCA
BBA001023	GGTTCTCTACCTGAAGCTTC
BBA001024	CCACTTGCAGTCTGTGGAAT
BBA001025	TGAACCAGGACACTGCTTGT
BBA001091	AAGTGGAACTGGAGCACTAG
BBA001093	ATCCTCCTACTCCAGCTTCA
REA000250	ACCACGTACTACCTAGTCTC
REA000778	GGTACTTGGATGGTGTTCGT
REA001143	GGAACTTGAGTCCTTGATGA
REA001280	GAAGAGGTCGTAGGAAGGAA
REA001281	GAGGTGCTTCGTCGTTGGTA
REA001282	GGAAGGATCTGGTACGTCCA
REA001284	GCAAGTTGTAGCATCAAGGA
REA001285	CAAGCAGACGATCAAGGATT
REA001286	CCTCATCTCTCTCTGGTCAC
REA001313	TCGTAGCATCCAGCAACAGT
REA001315	TCGAAGGTCGTTCACCAGTG
REA001334	AACGATCACAAGGAGCAGTC
REA001335	CACGACTAGCAACTCATGGC
REA001336	CTTGTGTCCACGAAGAACAT
REA001337	CTAGAGGTGGTCCTCCTGTA
REA001398	GAAGTAGAACGATGCAACGG
REA001399	TACGATGCACACTTGGTTGC
REA001403	GATCACAGGATCATGTTGGC

REA001792	TACTGGACGACGTACTAGGC
REA001793	CCTAGACGAGCTTCTGGTTG
REA001798	ACAGTCTCATGGTCCAAGTC
REA001799	ACAGCACCTCGTGTAGGACT
REA001800	ACTGCAAGGATGCATCTGGC
REA001801	CCTTGACACCAACGTGAAGT
REA001803	AGGAACCAGCAACGAGGTTA
REA001805	TACTCCTCAGATCGTACGAA
REA001806	TTGTCTGAGGAGCTTCAGGA
REA001807	CGTCGTCGACGATCCTCCAA
REA001808	CACCTTGTCAGGAGTACGTT
REA001809	CAGTTGTACGAGGTTGCAGC
REA001810	CGTACCTTCTTCTAGCAACA
REA001811	AGCTCCAGCTTCGAAGTTGA
REA001813	CTCATCCACTTGTGTGACGC
REA001817	ATGGATGGTCCTACCTTCTC
REA001818	TGTTCCAGGACGTCCTGCAC
REA001821	TACCTCGAAGGTCTGGATCG
REA001823	TGTTCTAGTGGAACTCAACG
REA001824	AGTTGAACCATGCACTCTCT
REA001827	GAACTGATGTGCAAGAGTCT
REA001828	GATGGTACCAACGACCTACA
REA001830	CAACACGACACATCCAACCT
REA001833	GATGTGCTCTGCACACCAGC
REA001834	CCAGTAGAACACTAGAAGCG
REA001836	AGATCGAAGACGAGTGAGTG
REA001837	GTAGGAGAGGTTCGATGGTG
REA001838	ATCCATGTCTGGATCAGCAA
REA001839	GGTGCTCCAGAACGTACTTT
REA001840	GGTAGGTACGTTGTTCTCCT
REA001891	GTAGCTTGCACTGGACGTCC
REA001892	CCACTTGTGTTCCACTGATT
REA001893	CGAAGAGGTGGAACGACCAA
REA001894	GTTGGTCGATCGAGTCCAAG
REA001895	TGTCCTTGTTGCACTCCTTA
REA001897	CACATGATGTTCTCCTTGGT
REA001899	AAGTCTAGTCACACGACACC
REA001902	GACCTAGCATGCTTCCTAGT
REA001903	AGACACGTTCGTGGTCGAGA
REA001907	CATCCAAGGTCTGGTCTCTT
REA001909	AGGTTGAAGGTGCAACATGC
REA001910	CCTGAGTGGTCCTTCTTGAA
REA001911	ACCTAGATGCTAGGAAGCAG

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REA001417	TGTGTACCTAGCTGCTTGGG
REA001419	TCTCCTGTGGAAGCAGCAGT
REA001557	TAGCACTACGTGATCTGAGA
REA001558	GTCTTGAACTGATCCTACAG
REA001710	GCAGCTGCAGCAGTCGTAGT
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REA001785	GGAGTGGTTGGTGAGAGAGA
REA001790	AACGAAGGTTCTGCTCTGGT
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REA001804	CGTGCTCCAAGCAGTAGCTG
REA001824	GTCTGATCCTACCTTCCATA
REA001828	AAGTTCTCCTGATGCTCATC
REA001833	CTGATCCACTGAGCACTTCA
REA001840	ACGTTCCAAGTCGTCATCGG
REA001841	GGTCACGATGCATCCTGACA
REA001842	TCGTAGCAAGTGAGGAACAG
REA001845	GGTGCTTGGTACGAACGTCG
REA001846	CTCGACCAACCTGACCTGAA
REA001847	TTGGATCGACAGGACCTTCT
REA001848	TACTTCGTCCAGTTCCTTGC
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REA001850	GGTGAAGTACGACAACTACT
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REA001855	CTGGATGACCAGAACTTCAT
REA001860	GATCGACTTGCAGACGTGCA
REA001861	AGCTACGTGAGAGAAGACAC
REA001865	AGTCTGGTGGTGACGACTTT
REA001891	GCTAGGAGCACCATCACGAT
REA001895	TGAGAAGGATCTCGTACCTC
REA001901	TAGCATCGTTGCTCCAGACA
REA001903	AAGAACTCTTCGACTCCAAG
REA001906	ACGTAGTAGAGCTACAAGTC
REA001910	CGTCCTACCAACCAAGCTAT
REA001911	GTTGCTCCTCCTTCTCGATT
REA001912	GACAACTGTCCTCGTACACT
REA001916	GCATGAGAACTCTTGATCCA
REA001917	CCTCCATGCTGAAGTGGAAA
REA001918	GGTACGACCATCAGTCCACC
REA001920	TACAGTTGTCTCTGGTCTTG
REA001931	ACCTTGAACAACGACTCCTG
REA001932	GACCAAGTCAGTGCAAGAGC

REA001913	GTAGACAAGTACCACTGGTC
REA001914	GCATGGAACTTCCTGCAGGG
REA001916	GATCAGGACTGGTTGGAAGG
REA001919	GGACAGAAGGATCTTCAGCC
REA001924	ATCTGAGTTCCTTGGTTCTC
REA001930	AACTCGTGTCGTCTCCTTCT
REA001933	TCTGTGAACATCCACCTTCG
REA001934	ATGTCGATGTAGTGGTCCTC
REA001935	GCAGTTGAACTCCACGTTGC
REA001937	ATGTAGAGTGATGAGCTTCG
REA001942	ACCAACGTCATCGTTGCTGA
REA002406	GACGTACAAGTTCTTGGACC
REA002407	GTTGTAGGACCAAGCAAGCG
REA002409	TCGAAGTTCAGATCGTGATC
REA002411	CTAGTGTGAAGTGGTCCATG
REA002413	GCAACAGCATCACAGATGTT
REA002415	CGTTCTTGAAGCTACGACAG
REA002419	GTACCTGATCTGGATCTTGC
REA002420	GGACTCTTCTCAACTGTTGT
REA002422	GAAGTGCTCGACATGGTCAC
REA002423	GTACTAGGACCTTCGTTGCC
Dummy A	ATCGTACAGACTCCTCACAG

REA001933	CTACACAAGTGCTAGTCTTG
REA001936	GTCTGCTGTAGCAACTCATC
REA001937	ACTGCTCAAGAGATCACTCA
REA001940	GATCCACACGTTGCACGTTC
REA001942	AGACCTCCATCGATGGTAGG
REA002341	TGTTCTCACAGCTTCCTACA
REA002342	ATCACAAGGAGATGGTTCTC
REA002343	CACCTTGCACCTTGCATCAC
REA002344	TGTTGTCGAGTCCTCCAACT
REA002345	ATCCACACCACGACATCTAA
REA002346	CATGTGAAGAACCTCGTCCC
REA002347	TCTCCTGTCCAACAGTCCTT
REA002348	GTTGGACAGCAACCAGTGGT
REA002349	GTAGGTACAGGTGAGGTACT
REA002350	AAGATGAGGAGTGCAGTACA
REA002351	TACCTTGAAGCACGATGGAA
REA002362	ATCATGTCCTTGGATGGACT
REA002363	GATGCTGATGAGTGCAACTA
REA002408	TACGTCAACGTAGATGGTGA
REA002410	CGATCTGACAGTCCAAGGTA
REA002411	CCACGATCTCCTACAGACTT
Dummy B	CCTCGTCCTGATGTTGCATC

BB C	**Tag C codon**
Blank	CCAACTTGGAGGTTCATGCG
REA001415	TTGGTTCTGACACTGTAGAC
BBA001092	ATCAACCTACCACCAGGAAA
REA001332	TTCTCACGACAGCAACCTTG
REA001938	CTCTCTTGCAGCTACTGAAT
REA001939	AGTCAAGTCAGAGTTCGTAC
REA001944	TAGATCGTCACTGACGATCC
BBA000008	GGACGTGAAGGACATCACAG
BBA000029	CACTACTTGTTCTACGTGCC
BBA001023	ATCGTTCCAGTCGAGTTGAT
BBA001024	ATCAACCACCTCTACCACCG
BBA001035	AAGCTACAACAGCAGCTACG
REA000250	CCAGTAGGTGATGCAACGTA
REA000772	AACAGGTCCACAACAGATGG
REA000778	CCATGTCGTAGATCGTTCAC
REA001143	TCATGTCTCGTAGACACTGC
REA001281	GACGAAGCACAGCATCCATA
REA001282	GCTGCTTCTGAGGAGGATCC

BB D	**Tag D codon**
BBA000895	TAGTGGTTCACGTGACCTAT
BBA001041	ATGTAGTCATGCTGTCCACT
REA000894	CCTTCCAGTACATGCACTAT
BBA000100	GATCCTCCTTGTACCTAGTG
BBA000139	TGAGGTACCTTGTACTCTCA
BBA000837	ATGGACGAGTCTGACGTAGC
BBA000849	TTCGTTGAGGAACCTCACGG
BBA000893	CTCATGGTTCCTCCTACTGT
BBA000894	GTGTTCGTTGGTGACTCGTG
BBA000903	CTGTGGAACGATGGAGGAGG
REA000194	GCTCTTCCTTCGTCCTTGAT
REA000892	CCTACGATCCACGAAGCTTC
REA001101	GGATCTACCAGCTTGTCTTA
REA002259	ATGCAAGTTGGTGCTGACTC
BBA000031	TACAACGTCGTGTAGTCTCC
BBA000820	GCAACTACCTGACCAACCAT
BBA000828	GCACGAAGATGTCACTGGTT
BBA000829	GGTTCCAAGTGTAGGAACGC

REA001284	GCAACAGAACTACATGACCG
REA001315	GGACAGCTTCGATGCTTCAT
REA001331	ACCTAGTGGTACATCTTCCT
REA001334	CGTGTAGAACCACGTTCGAC
REA001337	GTGCTACCAGAAGGATGCAA
REA001407	CCACACAGGTCTCCTACATG
REA001414	GTTGAGTCGATCCAGAGTAG
REA001421	GGTTCCTTCCTGAGGTTCGA
REA001552	ATCGTCCAACGAAGCAAGTT
REA001557	AGTACGTTGCTAGTTGACGC
REA001558	GGACCTACCTTGCATGAGGA
REA001768	GATCGACTTGAACTTCACCC
REA001779	TCAACGAACACCTGTCCACG
REA001780	GGTGAAGCAAGTGTTCAACT
REA001785	GCTAGATGTGAAGGTCCTAA
REA001790	AAGACAGTACCACGATGCTA
REA001793	GTTCGTACCACCTTCAAGAC
REA001801	TGGAGTCGTACAGAAGCATG
REA001815	ACCTACAGTACCAGGTGGTG
REA001824	CGAGACTGTTCCTGCACTCC
REA001828	TACTCTGCACGTCAGTTGTA
REA001829	GCTCCTGATGTCCTGGTTGC
REA001833	TCCACATCCAGCTCGTGGTT
REA001838	CGAGCACCAAGCACTGTTGT
REA001840	AAGGAACCACAACCAACCTG
REA001841	GGATCCATCGTCTACCTCTA
REA001845	AAGATGGACTCTGCAACGTT
REA001851	TACTGACACTCGTTGCTAGA
REA001852	ATCTGATGGATCTGTGCTCC
REA001853	ACGAGTCTCTCCTAGGACAA
REA001854	TCGTTCTCGTACTTGTTGGA
REA001855	GCTTGTCTAGACGTTCTCTG
REA001856	TCCTGCTTCAACCTAGATGG
REA001857	GACTACCTGGATCGTACATA
REA001858	AAGCAAGGAGGTGTACGTTT
REA001859	CCTGAGCTCAGAGTGTAGCC
REA001860	AGTGAGTCCTACCAAGCATG
REA001861	TACGAGTGTGCAAGCATGTA
REA001863	CTCTTGACGTGTTGTGCTAG
REA001864	AGGAGCAAGCAAGGTACCTT
REA001865	CGTGTCCAGAGGTTGCTGAA
REA001892	CCTACTAGCAACCATGGTCG
REA001893	CTCACATGGTAGCACGATGC

BBA000830	TCCAACCAGCTCCTGGTACA
BBA000836	ACCTAGCTCACAAGGTGGAT
BBA000843	AACTTGTCCTAGACTACGAG
BBA000845	ATCAGGTGTACGACTCAGTG
BBA000846	CAGAAGCAACCAGTGGTCAC
BBA000847	TGACCACGTGGTAGGTCAGA
BBA000851	CGTCGTACTTGTTGCACGTT
BBA000852	AGTGACACGACATGCACGAA
BBA000853	CGACACTCTTGTAGTCGTGC
BBA000862	GGTTGGATCTCTCTGCTCTC
BBA000886	TAGGTAGCAACCAACGACGT
BBA000891	ACCATGGTCCTCCTGGAGAT
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BBA000896	GCAACTGGAGTGTGATCCAC
BBA001038	GACAGGTCATCAGTCGTTGC
BBA001039	GGACTGTGAACGTACACCTC
BBA001042	ATCCTTCAGTACGATCCATC
REA001095	TGATGATCTGTGGACGATCT
REA000068	ACGACTCCAACTGTCCTGGC
REA000402	CCTTCATCTGGAGATGTCGA
REA000556	TGGTAGTTCCTTCAGGAGTC
REA000736	AAGAAGCAGTCCTAGCACGG
REA000749	TGCTGGTAGACAAGACGATT
REA000893	AACTCTTCGACGTGACACTC
REA000898	AACAAGACGTGACGTTGCTG
REA000901	GATCTCTTGAGTGGAGTCCC
REA001004	CACCAACCTCAGACCTGAGA
REA001015	GGATGCACAGGTACAGGAAT
REA001022	TACCACAACCAGTCCTTCCT
REA001023	ATGCTGTCAAGCTTGTAGGG
REA001028	CTTGCATCAAGCATCGAGCG
REA001029	AGGATCCTGTCACTAGTGGA
REA001031	CTGCAAGCTAGACAACAGTG
REA001038	CGACCTCCACTGGTAGACCT
REA001044	TCCAAGACTACGATGTTGAG
REA001045	CCTCTGATGGTTCATCCAGT
REA001055	GATGAGACATGCTACAAGAG
REA001056	GCTGGAGGTGTTCATCAACA
REA001058	TGGAGTTCGAGTACGAGTCA
REA001061	AGTTGCAGACAGGATGAACG
REA001062	GTAGTGAACGACCACGAGTG
REA001069	TACGTCGTCCTTGCAGACAA
REA001070	GTACAGGATCTACGTTGAGC

REA001896	CACTTGTACGAGAAGATCAG
REA001901	CGTTCCACTCATCTGTGCTT
REA001902	CCTTCACGATCCTACAGTCA
REA001905	ATCTCAGACACCTTGATGTG
REA001906	TCAGGTCTTGGTAGGATCCT
REA001907	TACGTCCTACCAGTCCACGA
REA001909	CCATGCTACCAGTACCACTG
REA001916	GGACCTTGCTTCCACACGTC
REA001917	CACCTGACTAGACAACAACT
REA001918	TTGGTCGAAGGAGTCGTGAC
REA001920	TGCACCTGCACTCACGTCCT
REA001923	ACAGGAGCAAGGAAGCAACT
REA001931	AACTGGAACTCAAGACAGAC
REA001932	GAAGCTGAGACCATGAGAAT
REA001933	CTCGAAGTAGTGTTGATGGC
REA001934	CCATCCTCGATCTCGTGTTA
REA001935	AGTCCATCTCGTGGAACTTC
REA001937	TGCATCCATCATCACTAGGC
REA001940	TAGATCCTGTCAAGGTTGCC
REA001945	GCTTGGACTGTGCTGATGCG
REA001946	CGTAGTAGACATCTCTAGCA
REA001961	ACTGTTCTCGATGCTAGTAC
REA002341	CTCTTGTCAGACGTGCTTCG
REA002344	GCAGAAGTAGACTGTCCACG
REA002345	TCGAGTGTGTGTACCAAGAC
REA002351	TTGGATGCAGTCCAGGAGAA
REA002407	CATCTCCAGTGTCGAGCATG
REA002409	TACGTGACAAGGATCTTCGC
REA002411	TGACCATCACCTTCTGCATT
REA002416	AAGCACAAGCACTGAGTCGG
REA002444	TCCTGTCACTCCAACCTCGG
REA002446	ATGGAGAGTAGTCTCCTGGT
REA002447	AAGAGATGCTGACTGGTAGG
REA002448	TCTCTCAAGCTACGTTGGAC
REA002449	ACCTTGGAAGTACCAAGTTG
Dummy C	CGTGCTACCACACTCACAAT

REA001071	GTGCTCAACAGTCAGGTGCC
REA001072	GCTTCGTACGATCATGTACC
REA001085	GGTGTGTTCAGAACAAGCAC
REA001090	CTCGATGGAGGTTGTAGCAC
REA001093	TAGCACGTTGAGCTACGATC
REA001094	ACAGCAAGTTCGTTCCTCTA
REA001097	TGTTCGTTGTCAGCAGTTCG
REA001100	TCATCGAGCAAGGTGTTCGC
REA002260	CGAGTCTTCAACTTCCAAGC
REA002262	TCCATGTTCGTACGACGATG
REA002264	GTGTACTCCAGACTTCCTTT
REA002275	TACTTGCACCAGACTTGTAC
REA002276	AGTACAGGACAAGACACGTT
REA002279	CGATGAGAGTAGTGTCTACG
REA002284	GCAAGCTCAGAGCAGAAGTG
REA002292	CGTGACACGTGTTCAGCACG
REA002298	GTACGTGTTGCACAAGAGCA
REA002299	ACGATCACTACGATGAAGGT
REA002301	TAGGACGTAGCAGACAACTA
REA002303	TCTCAGTACGTTCGTAGTCT
REA002305	GCAAGCAACTTCGTTGGTAC
REA002307	GTAGAGAGACATCCAACCAA
REA002310	CCTGCTAGTGCTTCCTTGGG
REA002312	CACACGATCTGTAGTCCTGA
REA002313	ACACCAAGGTTCAGATGTGT
REA002323	TTCTACTGCTGTTGACCTTG
Blank	CCTGTCATCCTTCGTACTAT
REA001966	GTTCGAACAAGTCTCCAGAG
REA001969	GGAAGGACCAGACTGTCACG
REA001970	ACCTACAGACACACAGATGC
REA001973	TTCTGTAGGACCTTGGAACT
REA001978	GCTCCATGGATGTACCTTCA
REA001986	ATCCTCTCCATGCTAGAGGT
REA001989	GAGAAGGAGAAGGTCGTTGC
REA002000	TACGTGAGTAGCTACTGGAA
REA002003	TAGGAGTACTCCAGGATCGC
REA002004	TCAAGTGTCTGACGAAGCTA
REA002009	GTGATGGTAGACAGCTGTAA
REA002016	AAGTGGAGTTGGATGCACCT
REA002019	TTCCTGGTTGGACTCGTCGG
REA002020	CCTGCACGAACACTTGCACA
REA002027	TGAGTTGCTGCACTGTTGCT
REA002036	CTTGTCAAGCAGTCACTAGA

REA000798	TCACATGACCAGCACGTGCG
REA001466	CGATCAAGCTACAGAAGAAG
REA001475	TGGACTCTGTCGAAGGTACA
REA001508	CTGTAGCATCCACTCCATCC
REA001646	GACTGTGGTGACACCTGACT
REA002038	GCTTCGACAGACATCACTCG
REA002042	ATGGACAGTGGACACTCATT
REA002046	GCTTCTCCTGGTTGATGGTC
REA002050	CGTGGAAGGTTGAGCTCAAC
REA002065	ACATCTAGTCCAGGTGGTTT
REA002067	CCTCGAACCTTGCTACAGCG
REA002075	CGACGAGCACACTCTCTCAG
REA002076	ATGCTTGCACTGTGATGACA
REA002077	GTGTACTGAGTGCAGCATGG
REA002086	TACGAGCAAGGTAGCTGGTG
REA002088	CGTTCTAGGAAGTGAAGCTG

Table 2.5A Position A building blocks (reactants). The unprotected structures are shown. The amines were protected by Fmoc groups during loading. After loading Fmoc groups were removed(Same for Tables 2.5B; 2.5C and 2.5D).

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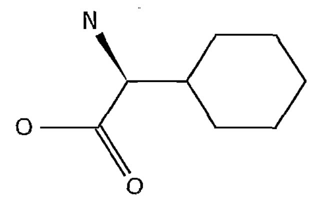

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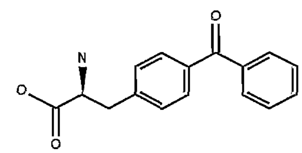

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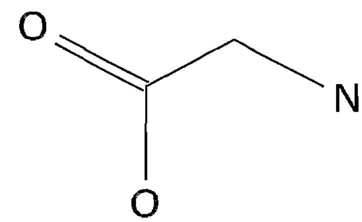

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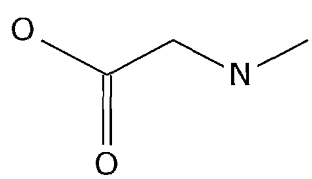

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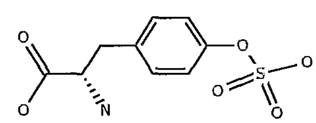

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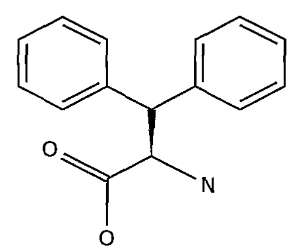

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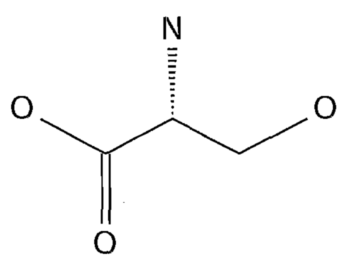

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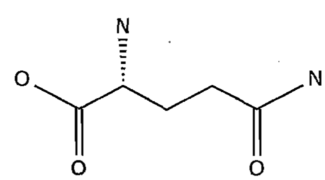

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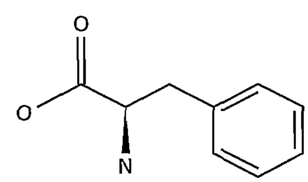

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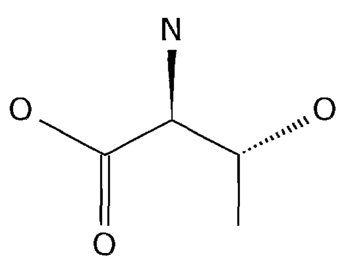

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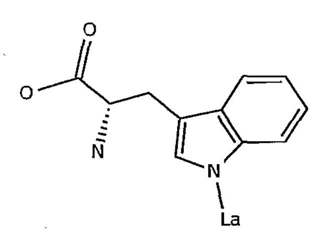

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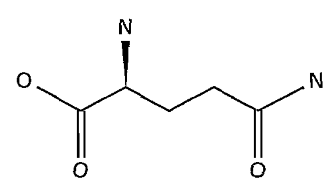

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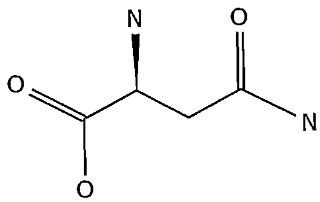

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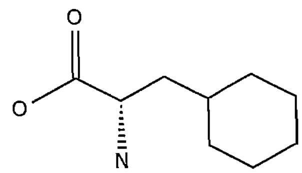

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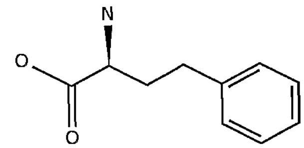

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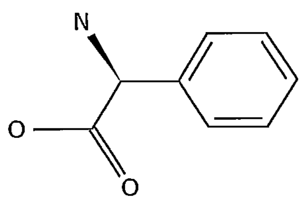

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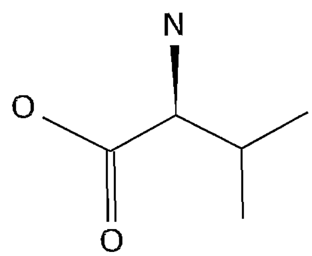

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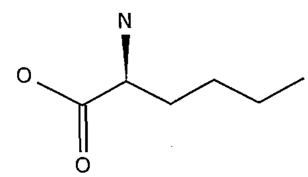

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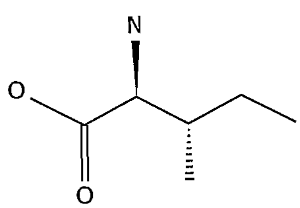

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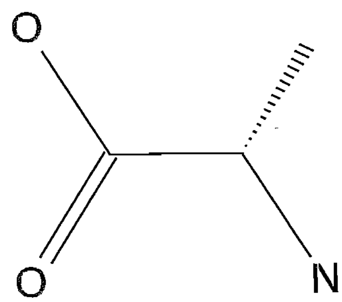

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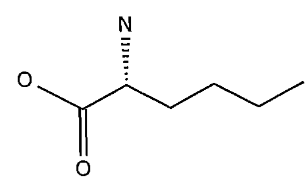

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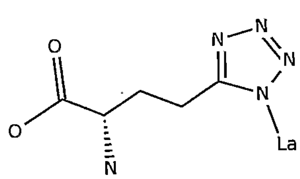

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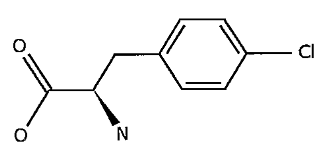

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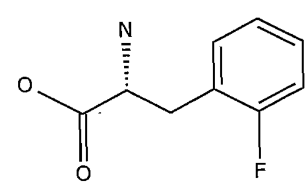

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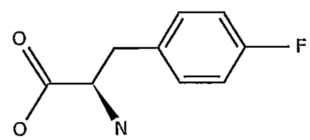

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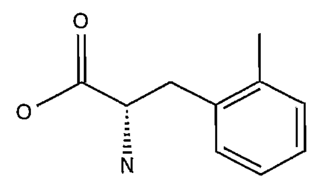

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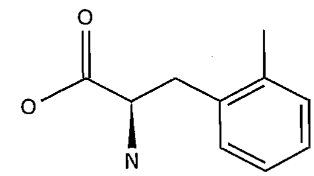

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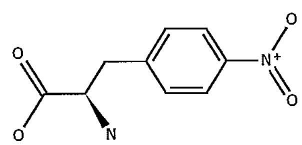

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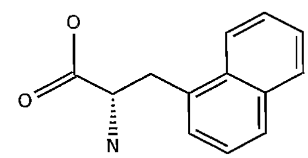

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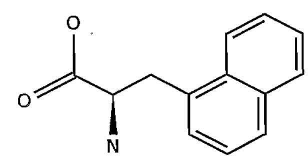

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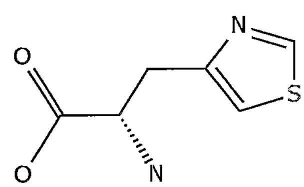

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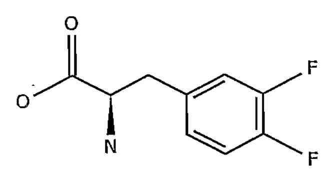

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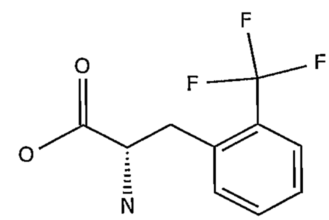

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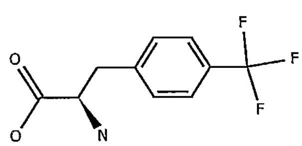

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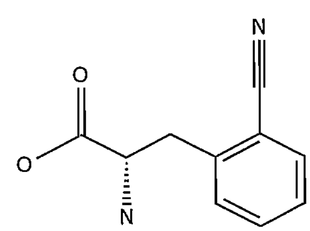

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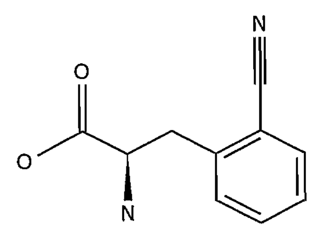

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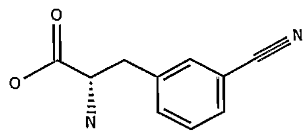

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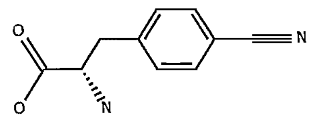

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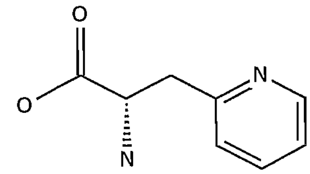

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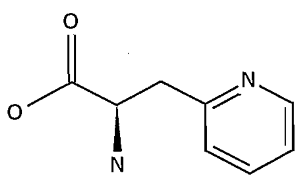

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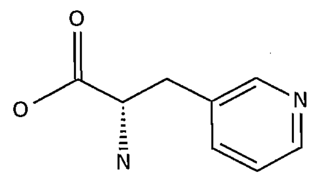

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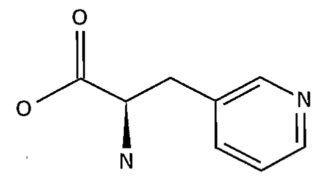

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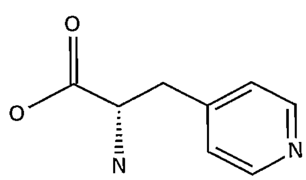

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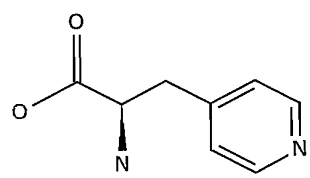

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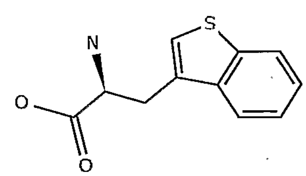

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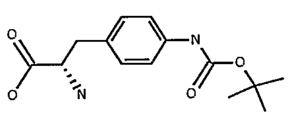

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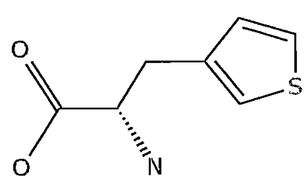

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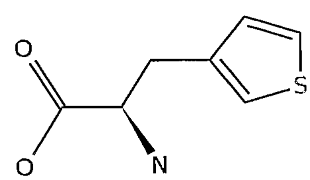

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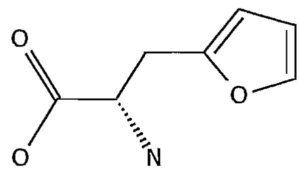

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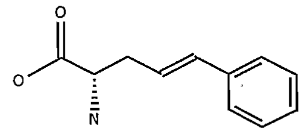

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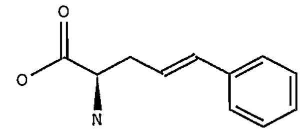

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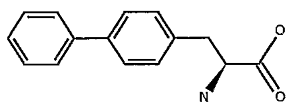

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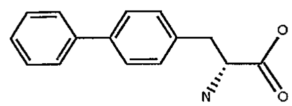

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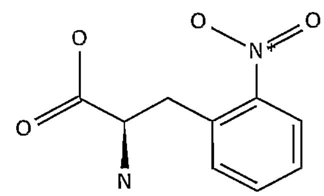

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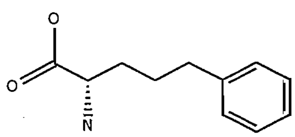

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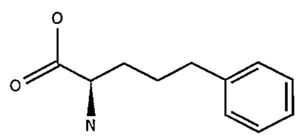

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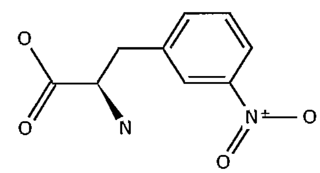

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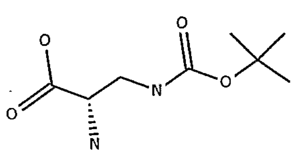

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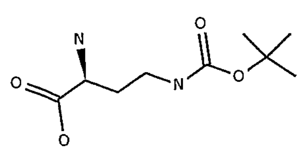

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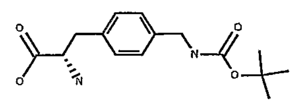

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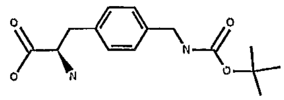

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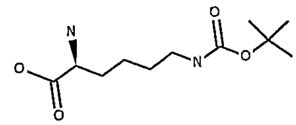

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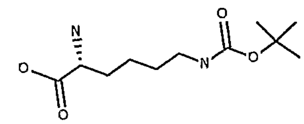

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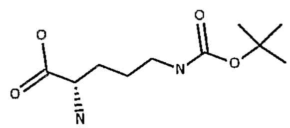

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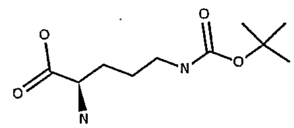

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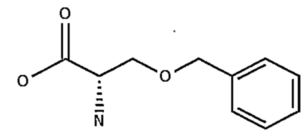

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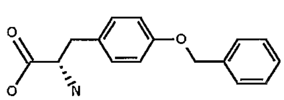

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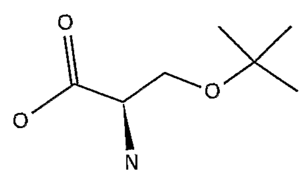

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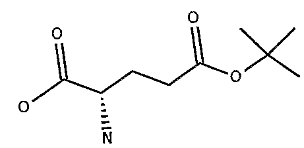

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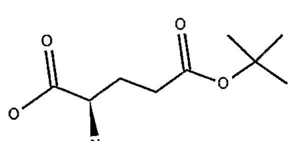

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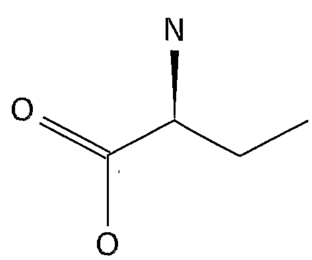

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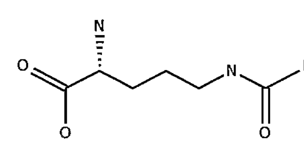

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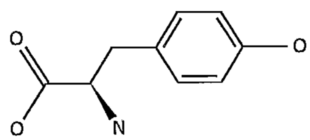

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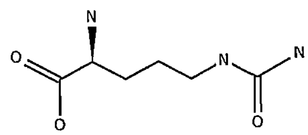

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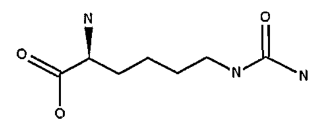

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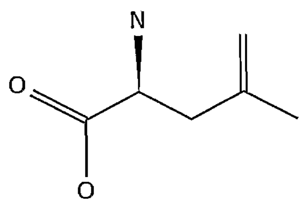

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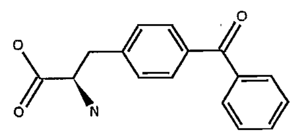

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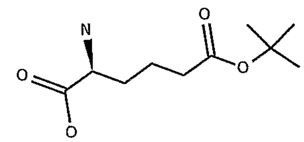

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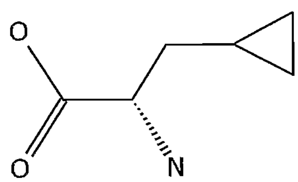

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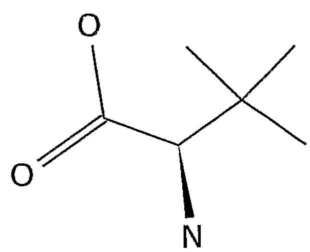

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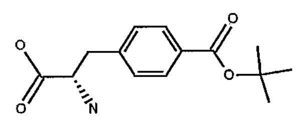

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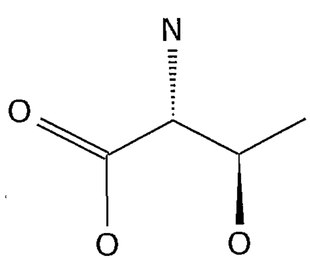

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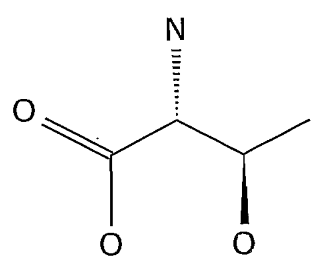

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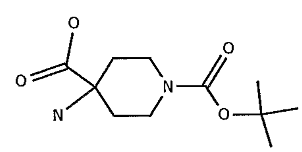

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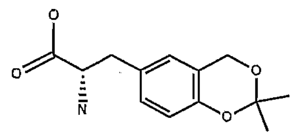

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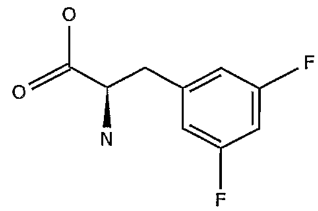

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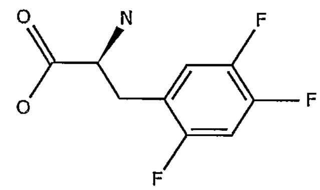

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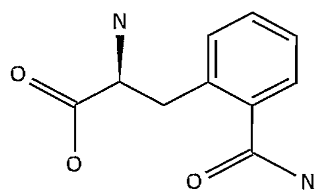

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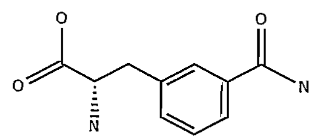

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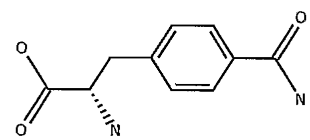

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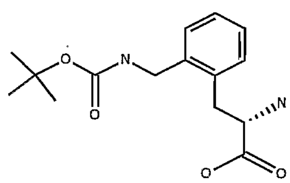

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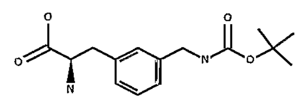

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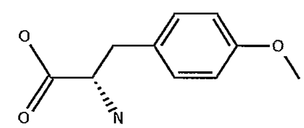

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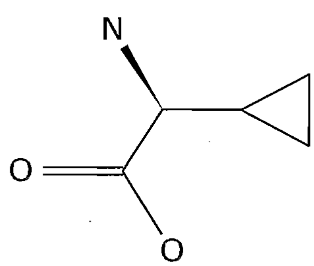

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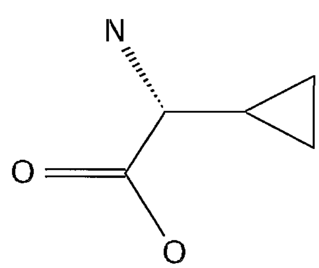

Table 2.5 B Position B building blocks (reactants).

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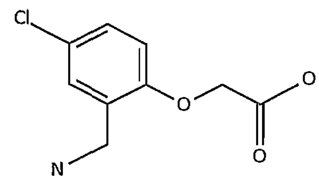

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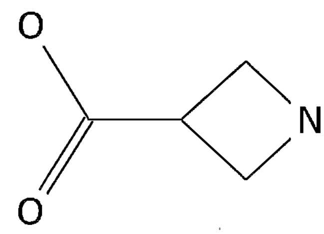

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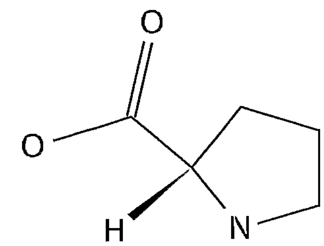

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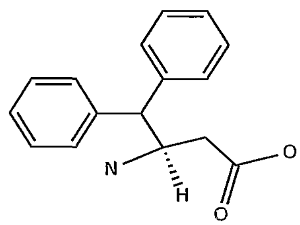

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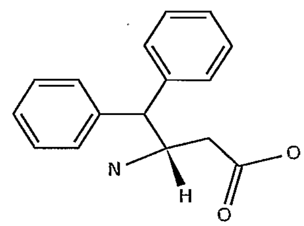

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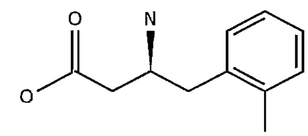

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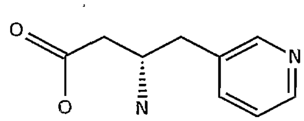

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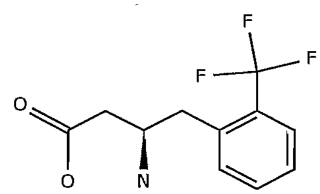

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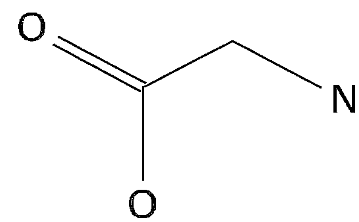

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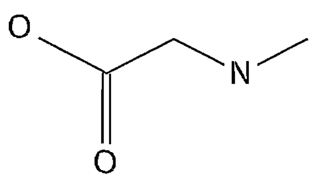

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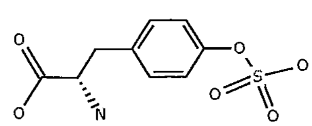

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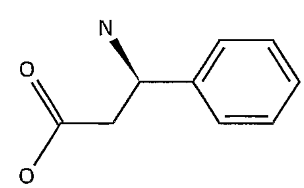

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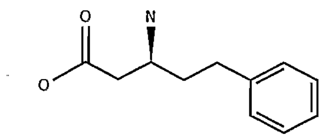

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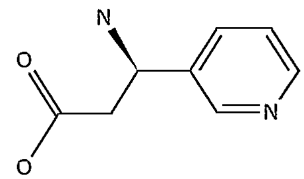

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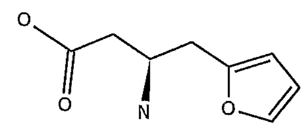

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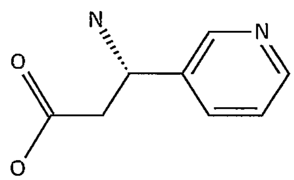

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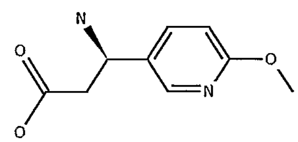

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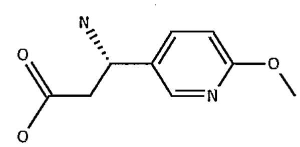

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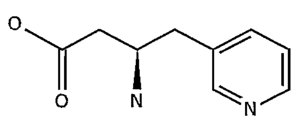

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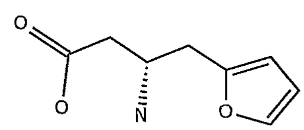

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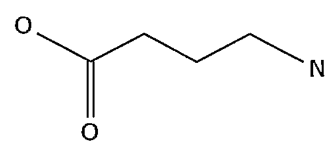

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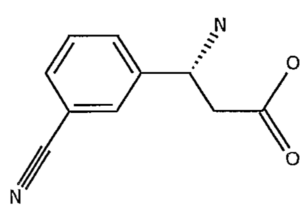

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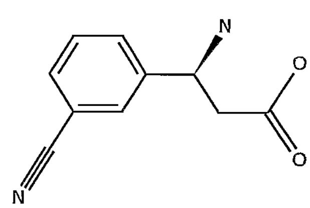

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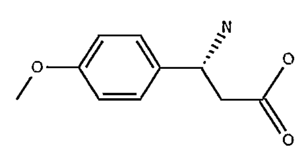

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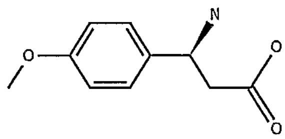

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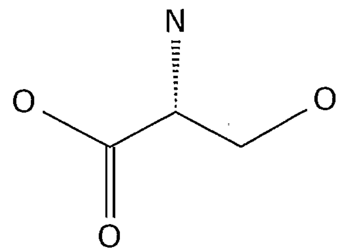

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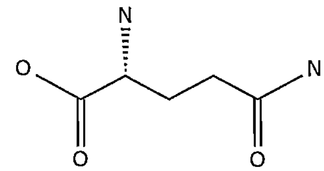

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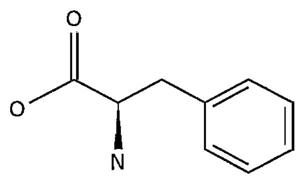

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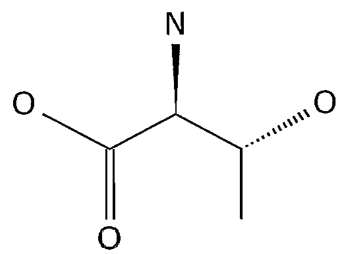

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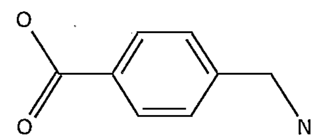

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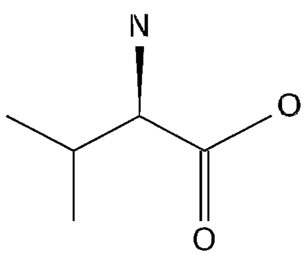

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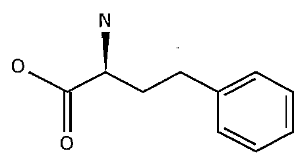

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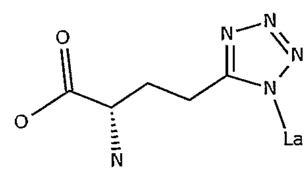

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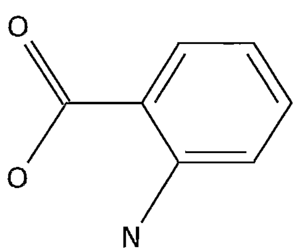

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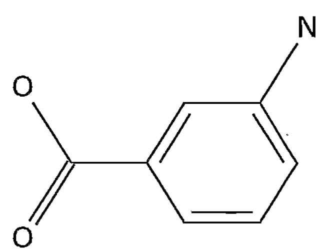

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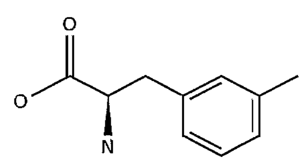

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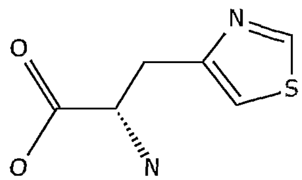

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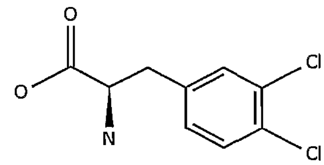

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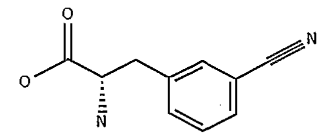

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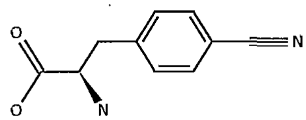

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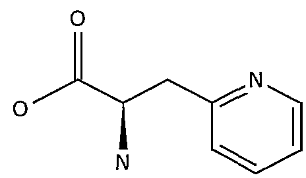

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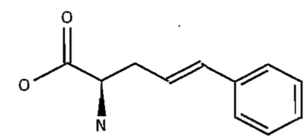

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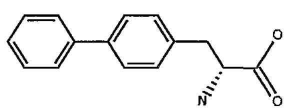

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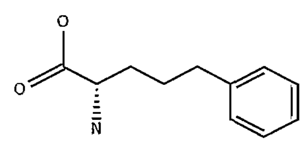

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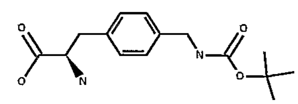

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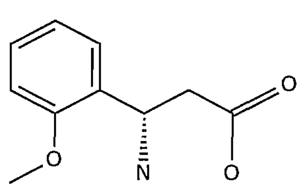

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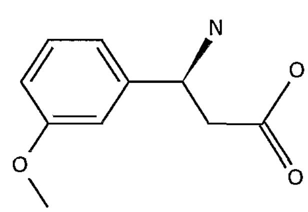

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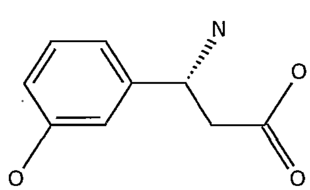

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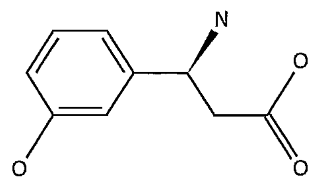

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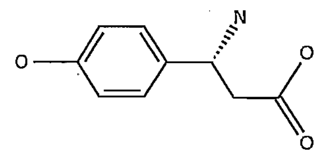

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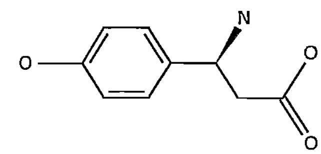

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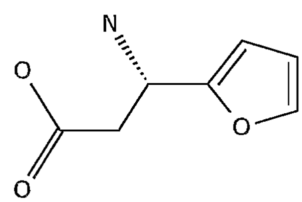

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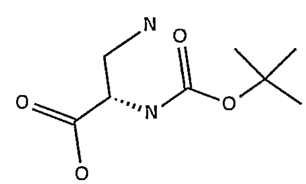

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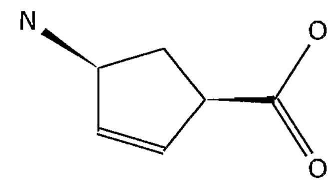

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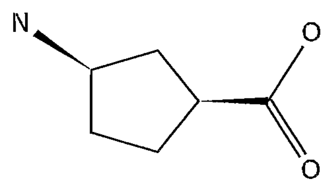

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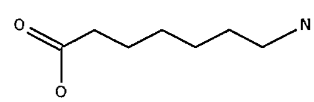

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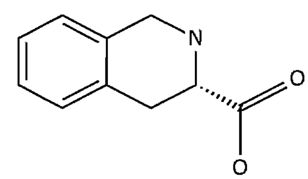

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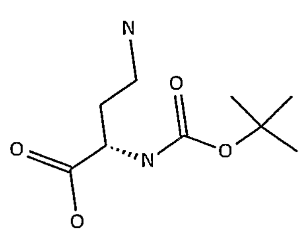

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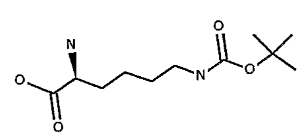

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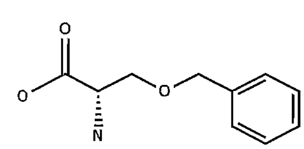

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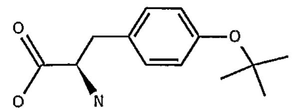

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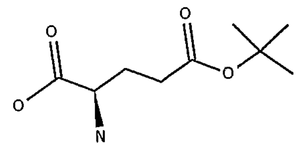

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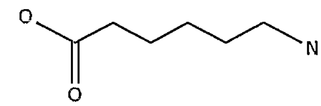

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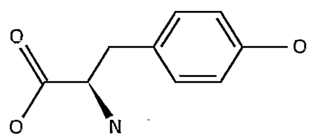

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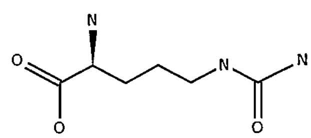

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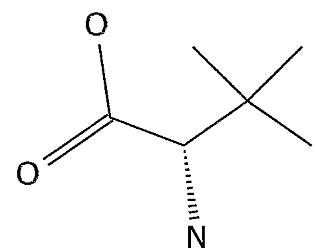

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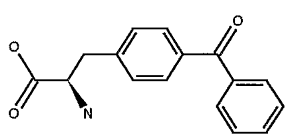

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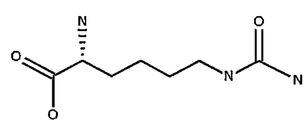

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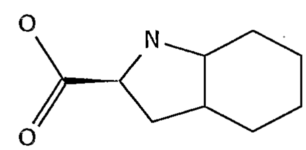

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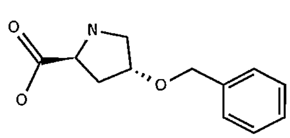

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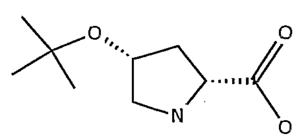

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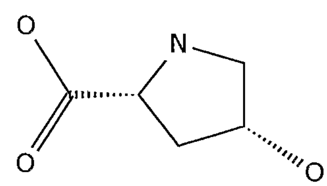

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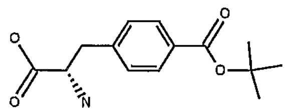

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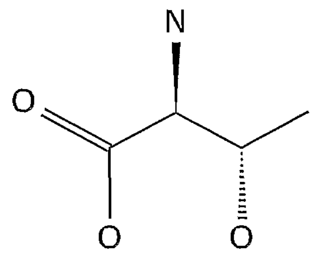

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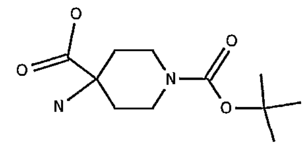

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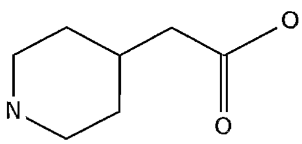

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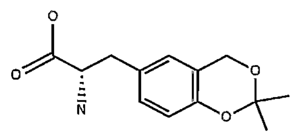

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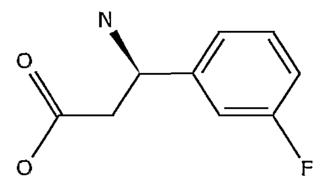

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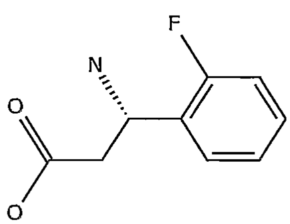

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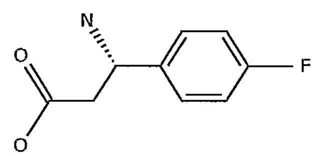

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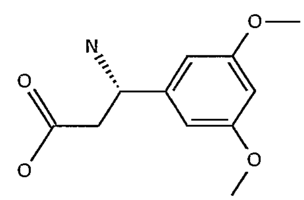

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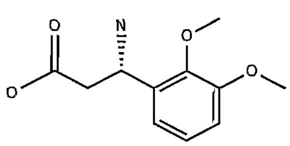

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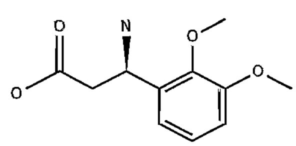

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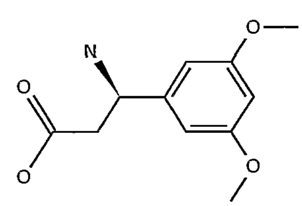

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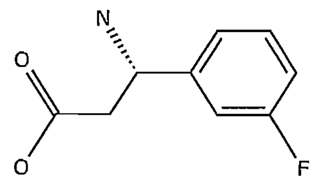

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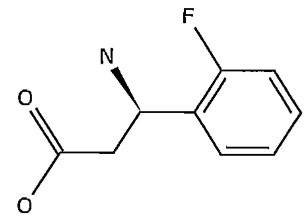

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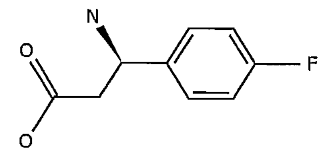

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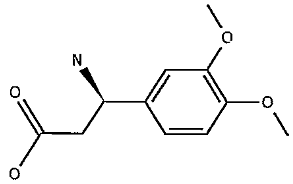

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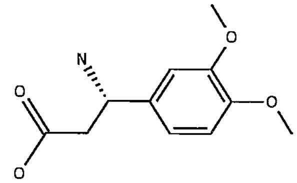

Table 2.5C Position C building blocks (reactants).

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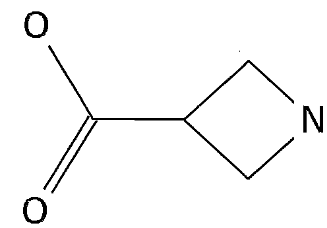

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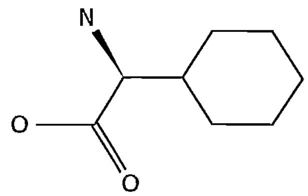

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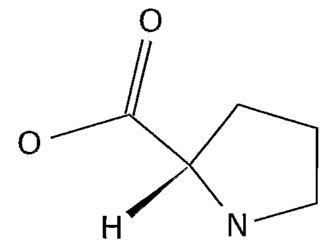

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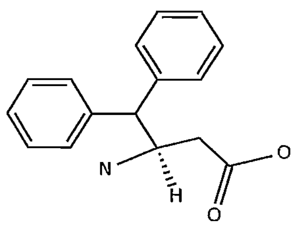

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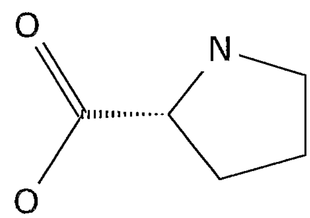

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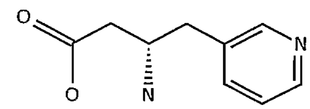

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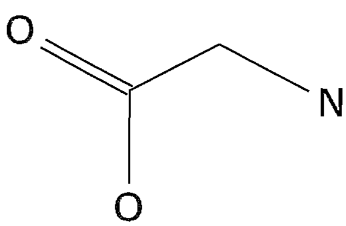

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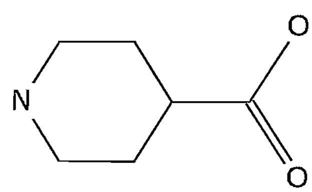

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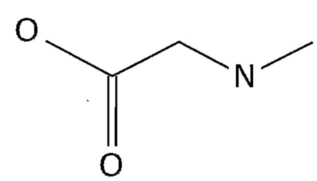

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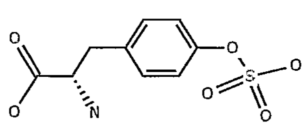

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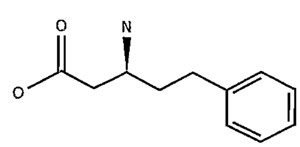

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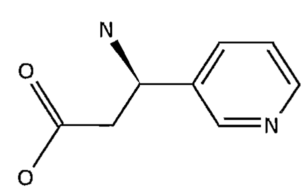

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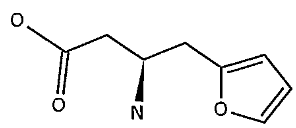

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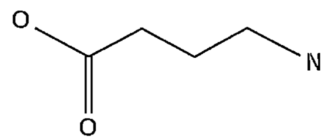

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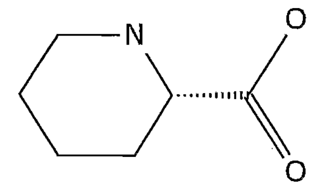

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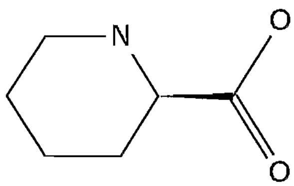

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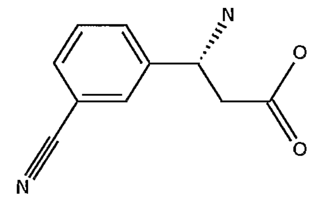

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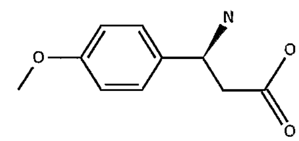

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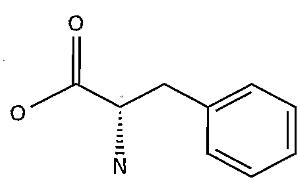

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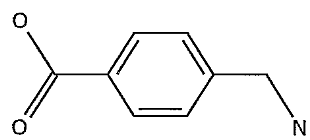

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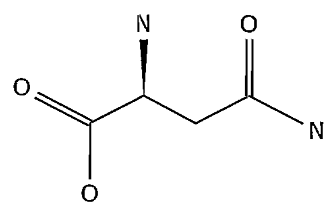

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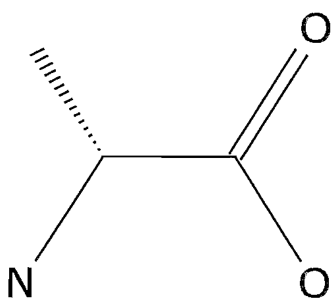

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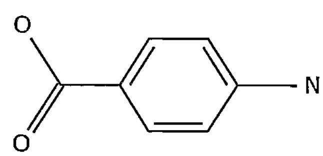

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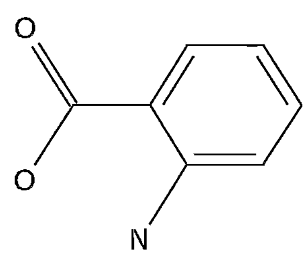

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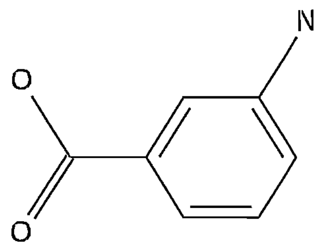

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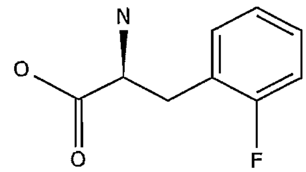

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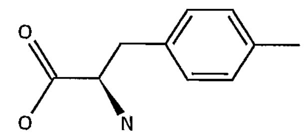

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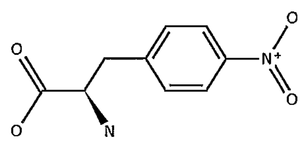

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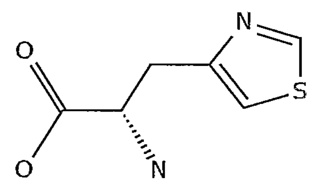

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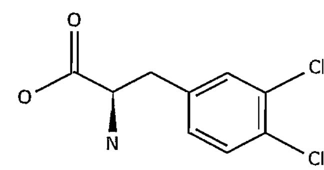

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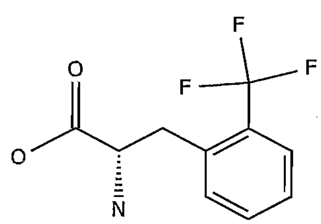

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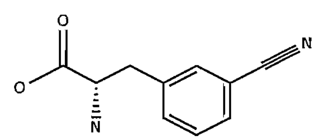

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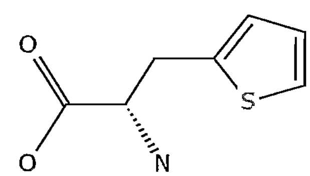

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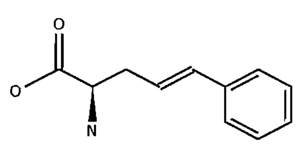

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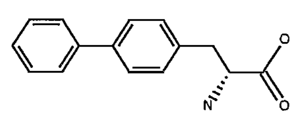

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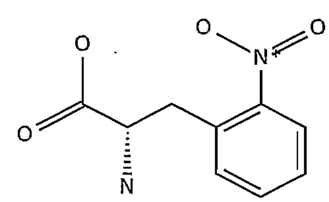

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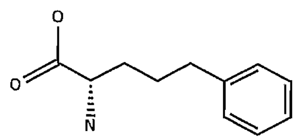

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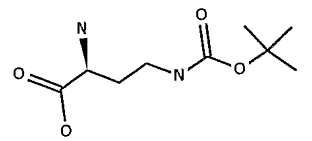

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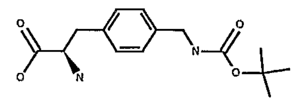

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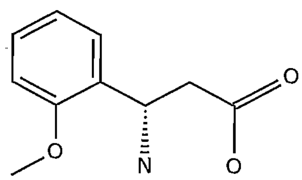

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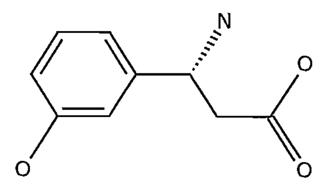

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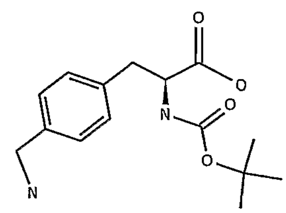

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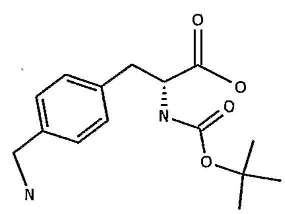

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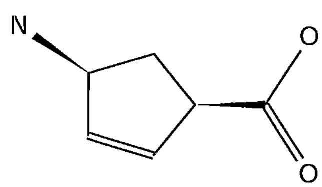

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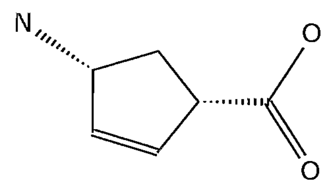

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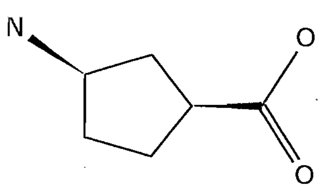

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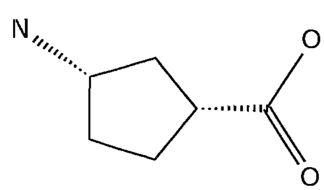

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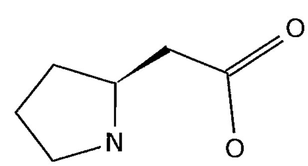

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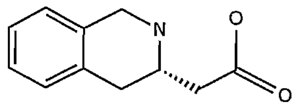

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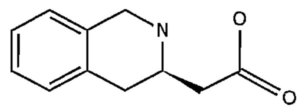

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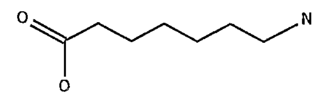

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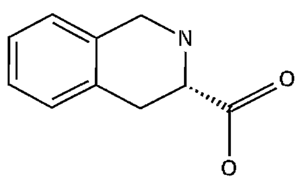

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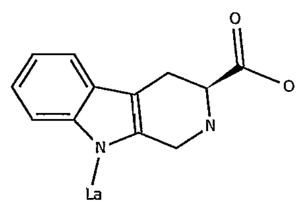

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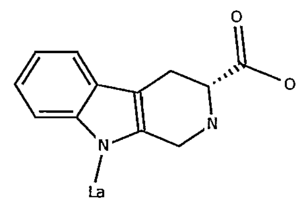

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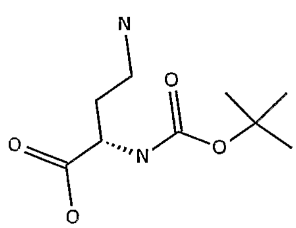

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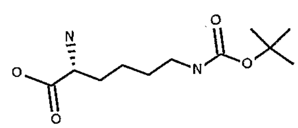

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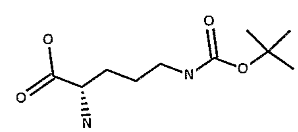

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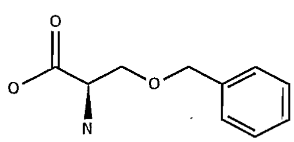

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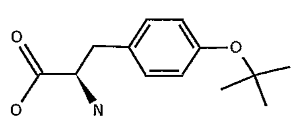

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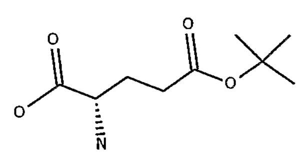

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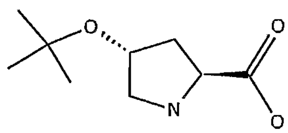

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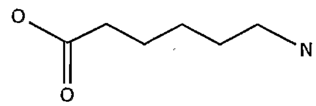

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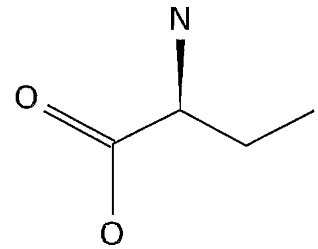

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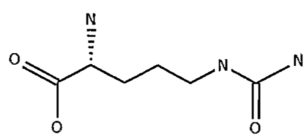

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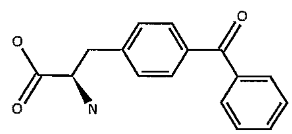

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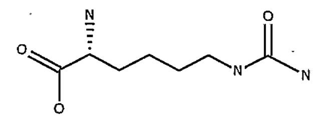

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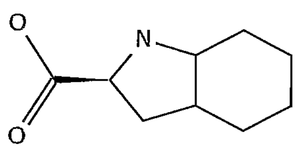

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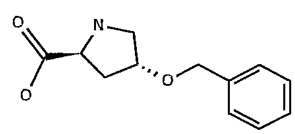

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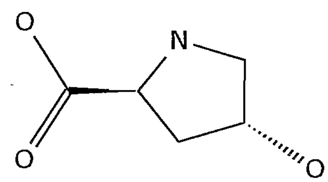

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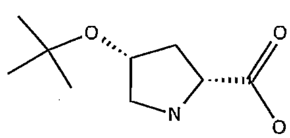

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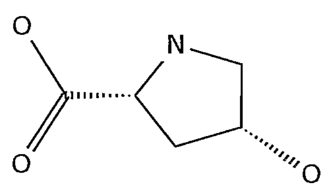

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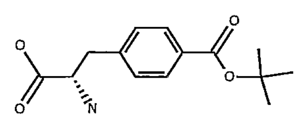

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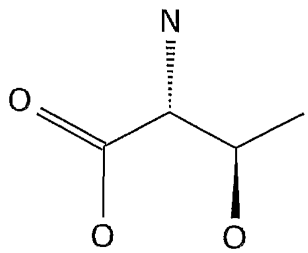

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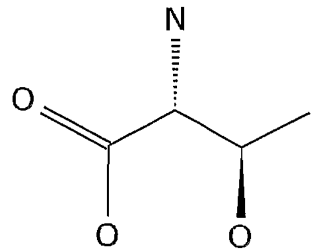

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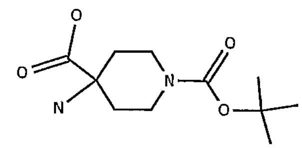

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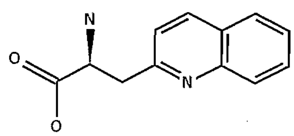

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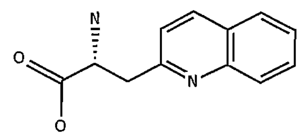

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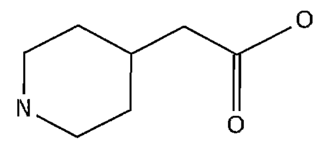

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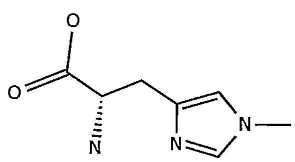

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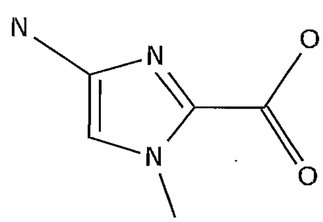

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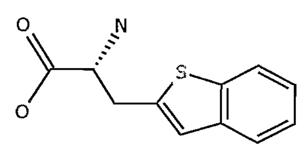

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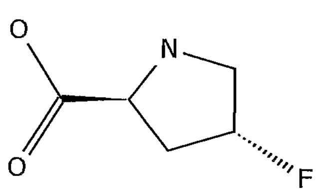

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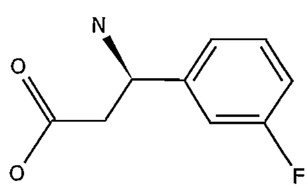

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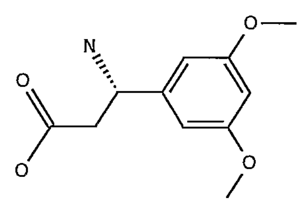

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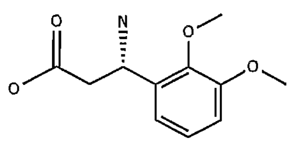

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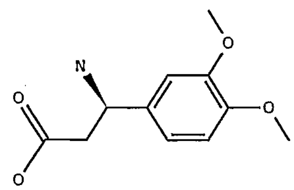

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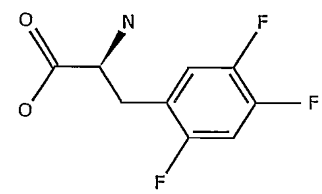

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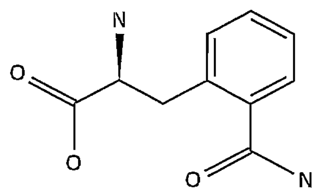

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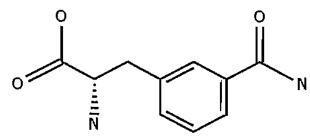

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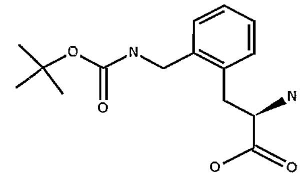

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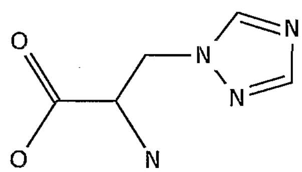

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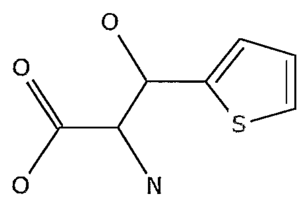

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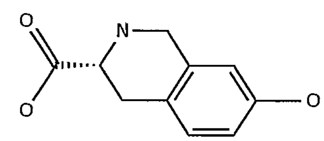

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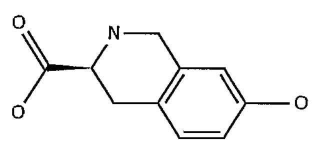

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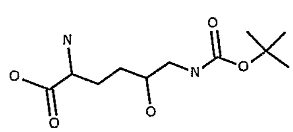

Table 2.5 D Position D building blocks (reactants).

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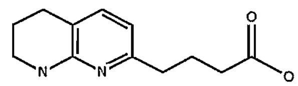

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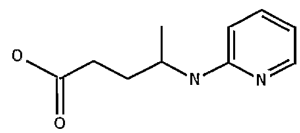

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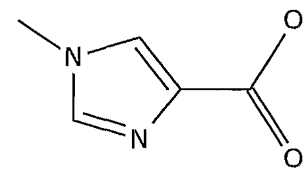

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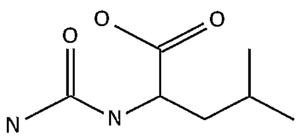

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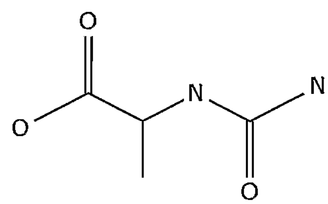

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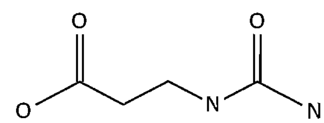

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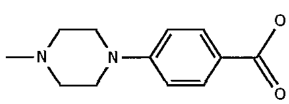

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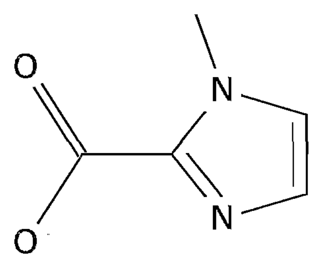

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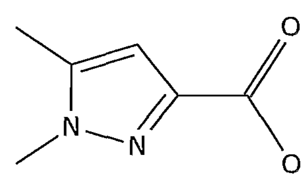

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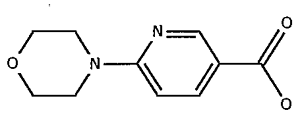

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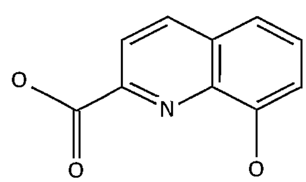

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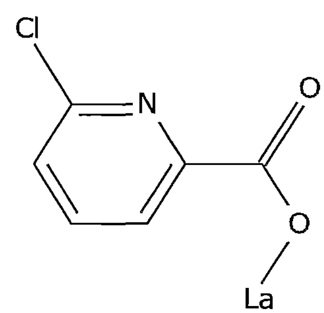

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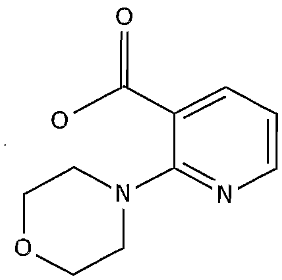

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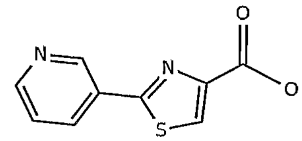

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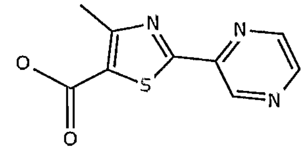

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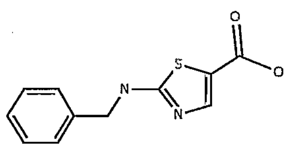

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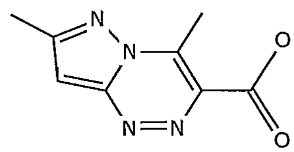

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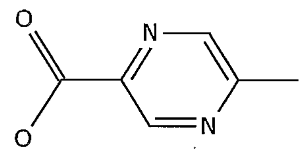

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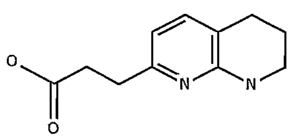

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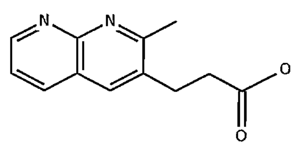

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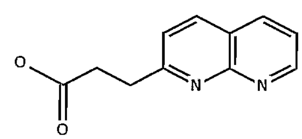

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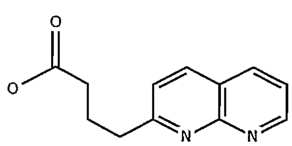

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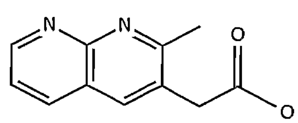

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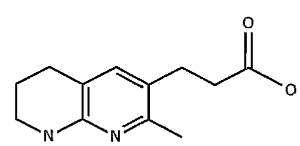

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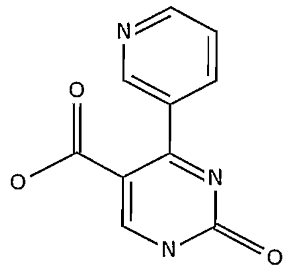

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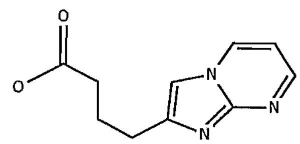

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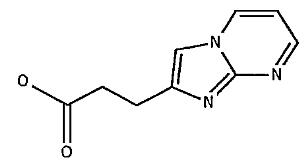

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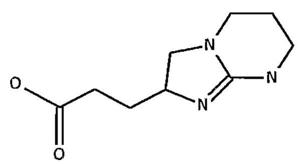

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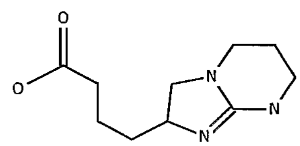

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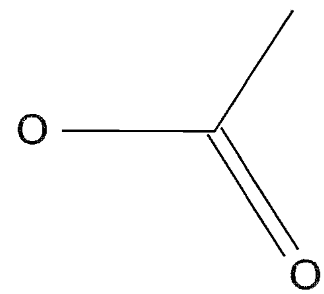

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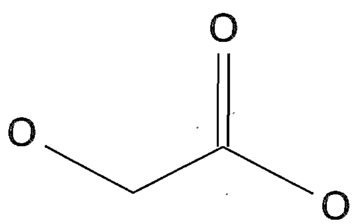

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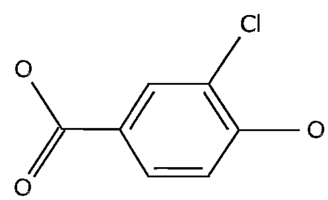

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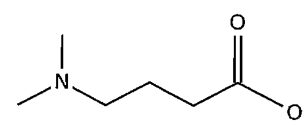

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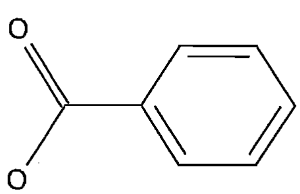

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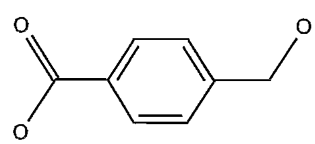

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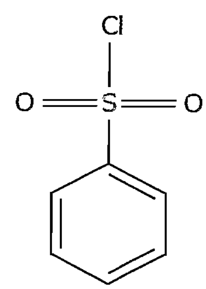

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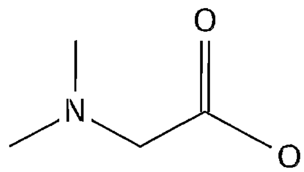

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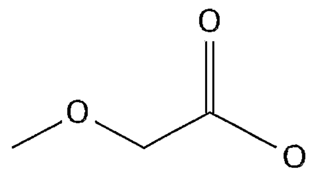

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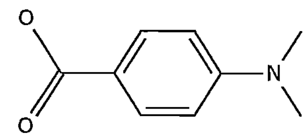

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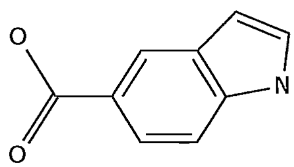

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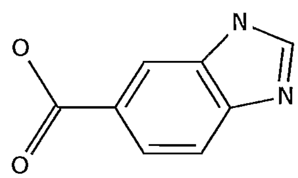

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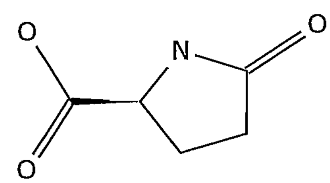

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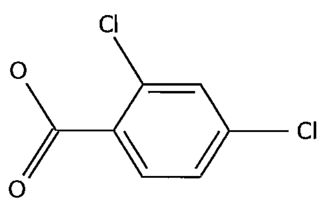

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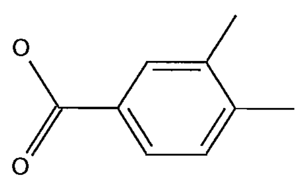

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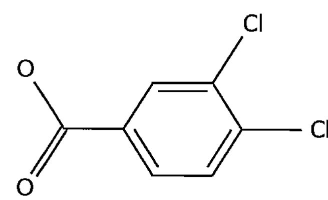

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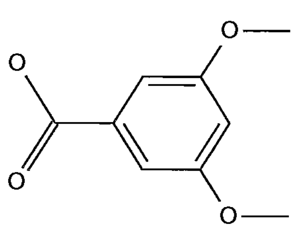

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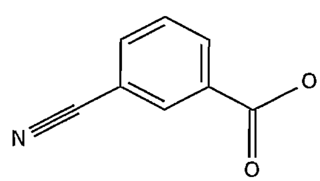

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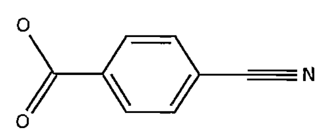

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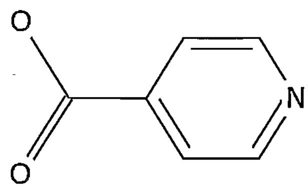

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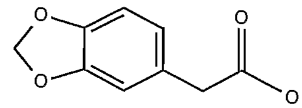

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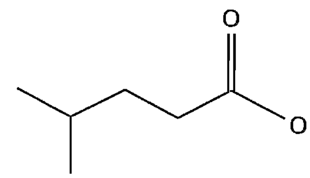

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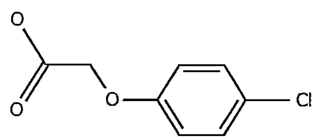

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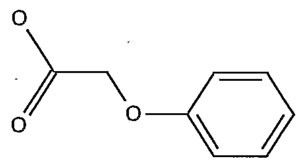

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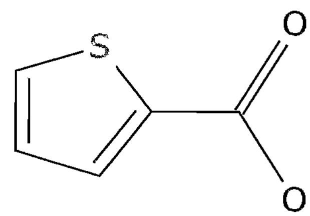

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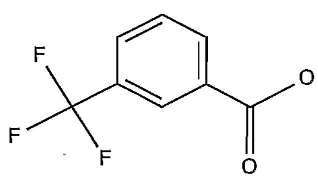

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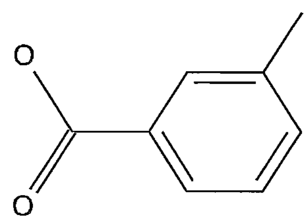

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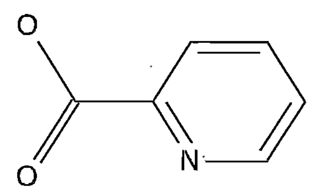

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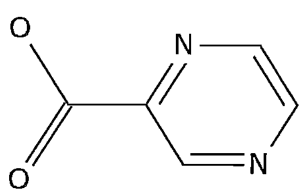

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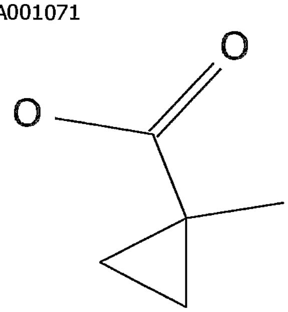

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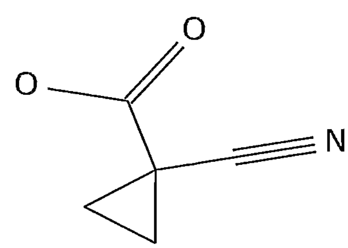

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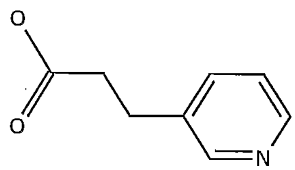

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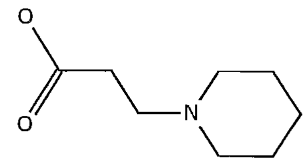

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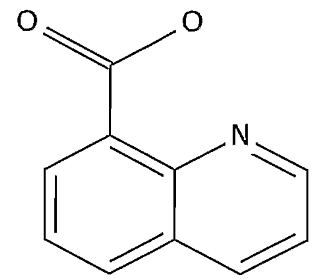

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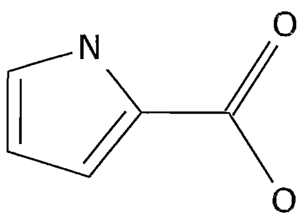

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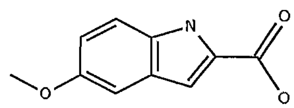

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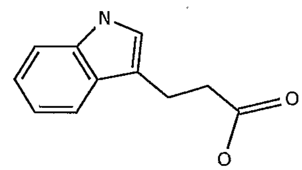

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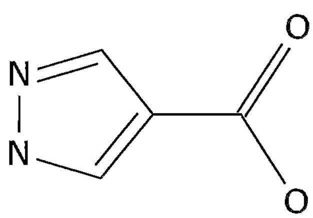

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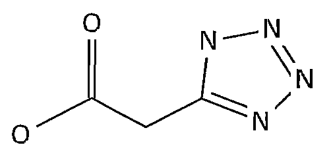

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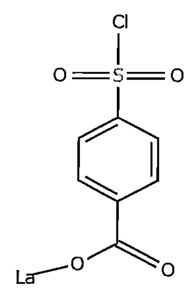

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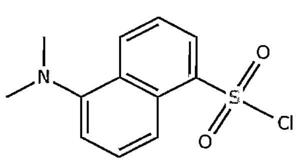

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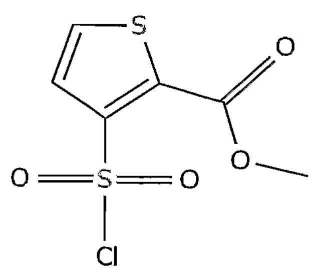

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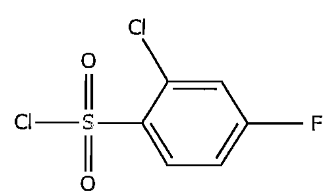

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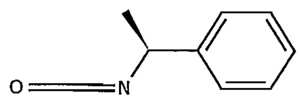

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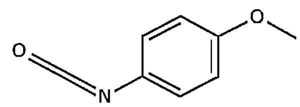

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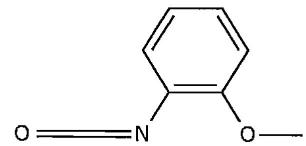

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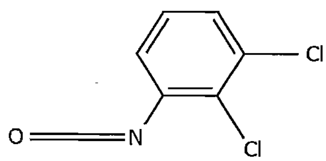

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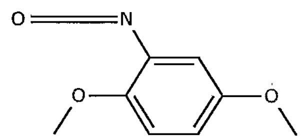

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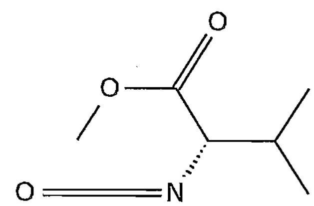

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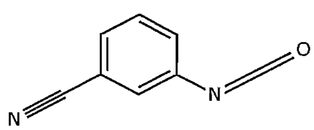

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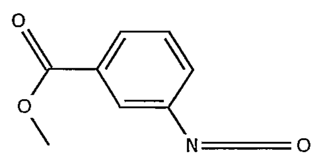

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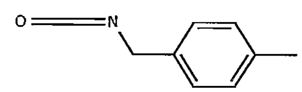

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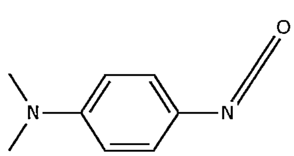

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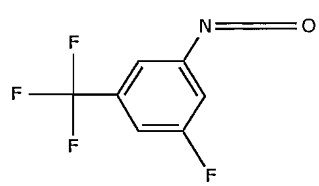

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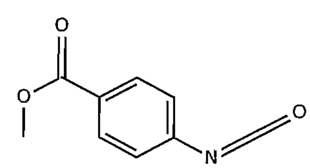

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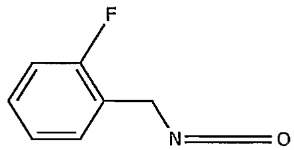

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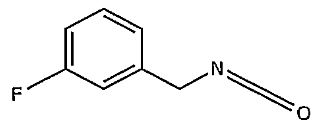

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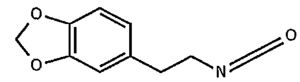

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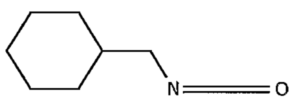

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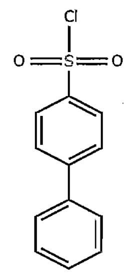

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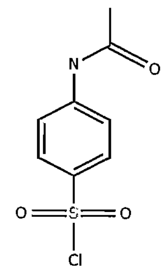

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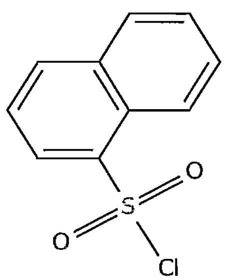

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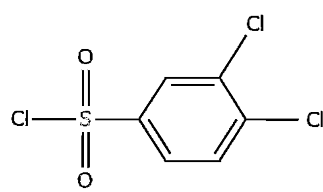

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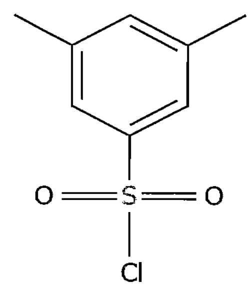

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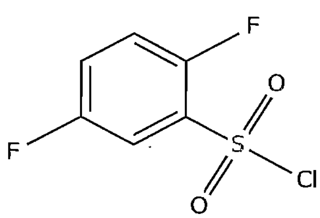

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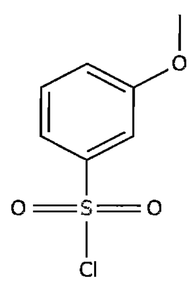

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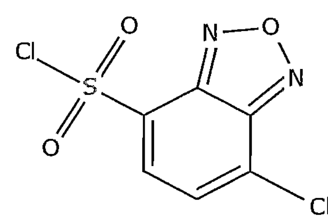

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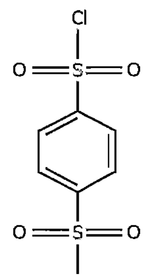

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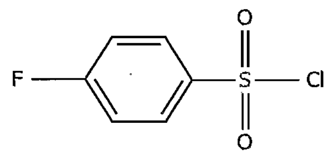

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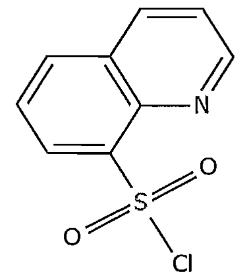

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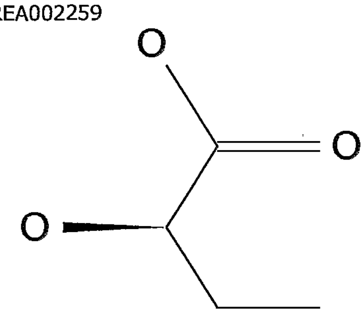

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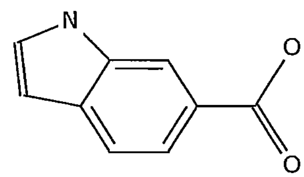

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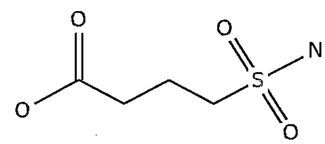

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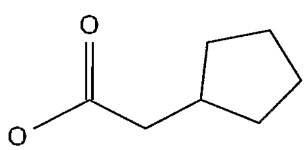

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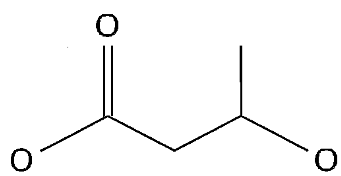

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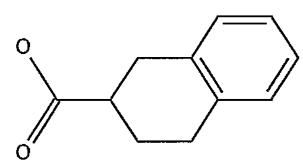

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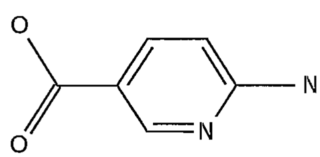

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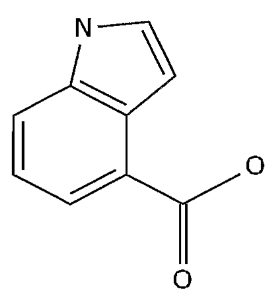
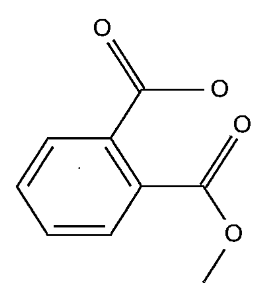
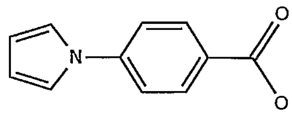


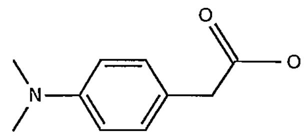
REA002292



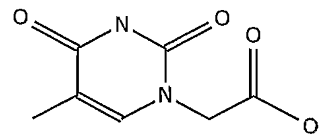
REA002298



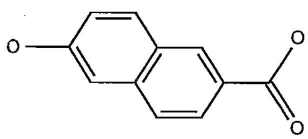
REA002299



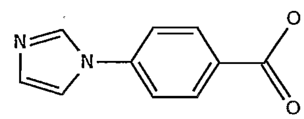
REA002301



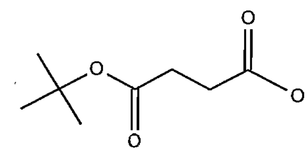
REA002303



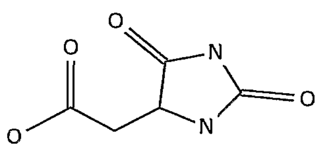
REA002305



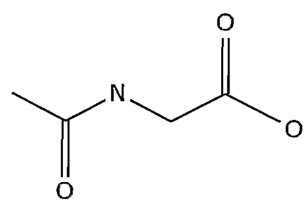
REA002307



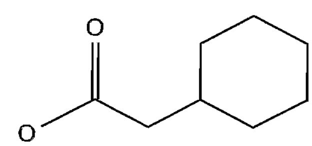
REA002310



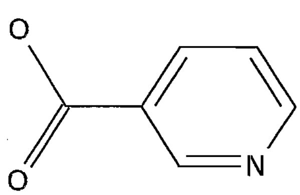
REA002312



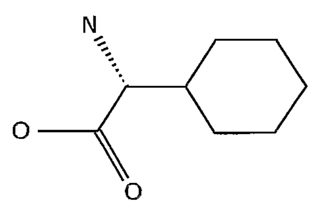
REA002313



REA002323



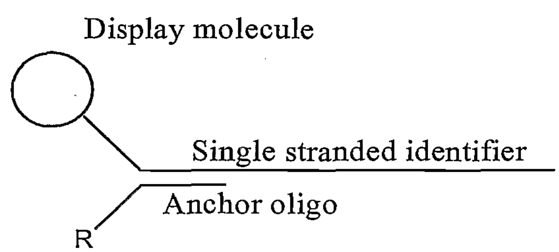
BBA000031



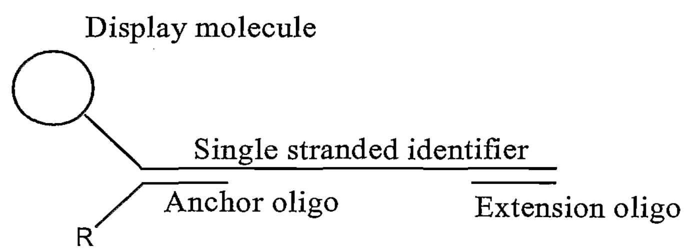
Example 3: Bifunctional complexes containing one or more display molecule(s) and one or more identifier(s)

A library is synthesized as described in example 2. At a stage where the bifunctional complexes containing a display molecule (D) are purified and have single stranded identifier oligos, an anchor oligo containing a display molecule (R) is annealed to the single stranded identifier oligos:

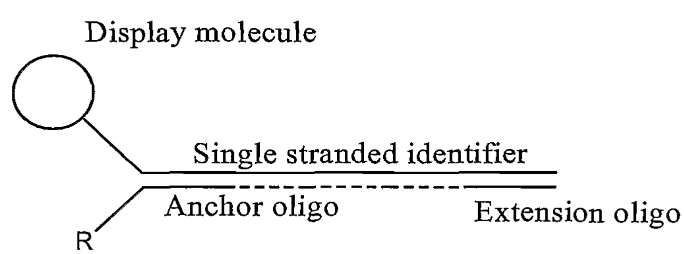
a)



b)

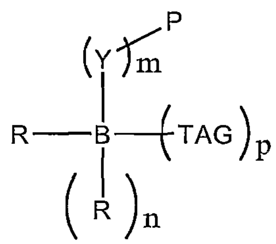


c)

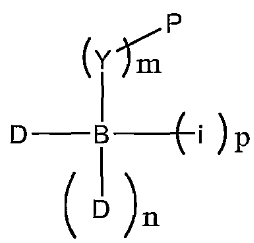


Then an extension oligo (b) is annealed to the single stranded identifier oligo of the bifunctional complexes. The extension oligo is then extended with an enzyme that does not displace or degrade the anchor oligo. The library is then used for selection. Using anchor oligos with different display molecules (R) it is possible to modulate the average affinity of the library.

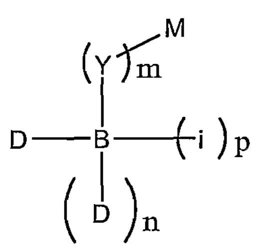
Alternatively the following display oligo is used during library synthesis:



The display oligo contains one or more (n) of chemical reaction sites (R), one or more branching linkers (B), one or more (m) chemical reaction site(s) (Y) protected by a protection group (P). Using this display oligo a library of bifunctional complexes is synthesized as describe in example 2. The resulting bifunctional complexes contain one or more display molecules (D) and one or more (p) identifiers (i):



The protection group (P) is then removed allowing a molecule (M) to be linked to Y:



Thus, properties of the bifunctional complexes, such as affinity for a target or target site, solubility etc. can be modulated by attaching to the chemical reaction site (Y) one or more molecules (M) which confer the desired property onto the bifunctional complex.

Example 4: Synthesis and affinity selection of a library encoding on the order of 65.000 scaffolded compounds employing quenching of reactants.

A library on the order of 65.000 DNA-tagged small molecules is synthesized using the building blocks (reactants) and tags described in example 2.

900 pmol Display oligo is added to each of 16 wells. In each well the display oligo carries a specific building block (position A building block).

Ligation of A-tags

10 µl buffer (120 mM HEPES pH 7.8, 40 mM MgCl2, 40 mM DTT and 4 mM ATP) is added to each well. 500 pmol double-stranded A-codons (e.g., the combination A-0001 and Ax-0001) is also added (See table 4.4A for tags and corresponding building blocks (reactants)). Annealing was then performed by a 80°C to 20° ramp in a PCR machine (Eppendorf Mastercycler Gradient). In one well 50 pmol double-stranded 5' phosphate 32-labeled A-codon is added. 1 µl of T4 DNA ligase (20 U/µl) is added to each well. Samples are then incubated in a PCR-machine with the following temperature profile: 25°C for 10 min, 45°C for 10 min, and 25°C for 10 min. The ligase is inactivated by incubating samples at 68°C for 10 min. 25 µl of water is then added to each sample. To allow verification of the efficiency of the following dephosphorylation step, a "Dummy A" codon labelled with 5' phosphor-32 is added to a sample. A thermostable phosphatase is then added to each sample and samples are incubated to remove free 5' phosphate groups. The samples are then pooled and precipitated using 0.05 volumes of 5 M NaCl and 50% isopropanol as described in example 2.

Ligation of B-tags

The sample is dissolved in water and distributed equally to 16 wells. To each well 750 pmol double-stranded B-tags is added and ligation and dephosphorylation is performed as described for the ligation of A-tags. After ligation and inactivation of the enzyme, the samples are lyophilized.

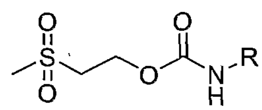
Load of position B building blocks (reactants)

Each sample is dissolved 5 µl 200 mM Na-phosphate buffer pH 8.0 or 100 mM Na-Borate pH 9.0 or 100 mM Na-Borate pH 10.0 according to previously identified reaction conditions. To each well is added add 4 µl solution of a building block (100

mM in dimethyl sulfoxide). For each well 0.72 µl 0.5M DMT-MM solution in water is mixed with 0.28 µl 200 mM Na-phosphate buffer pH 8 and added to the well. The wells are then incubated at 30° C for 16 hours in a PCR-machine (Eppendorf Mastercycler Gradient). Then an appropiate quenching reagent, e.g. piperidine, is added to each sample to ensure that all reactive species are rendered unreactive. The samples are then pooled and precipitated using 0.05 volumes of 5 M NaCl and 50% isopropanol and washed with cold 70% ethanol.

Msec deprotection

Primary amines of position B building blocks (reactants) are protected by Msec groups:



Scheme 4.1 Msec (2-(methyl sulfonyl) ethyl carbamate) protection group used for protection of primary amines.

Msec protection groups are removed by dissolving the material in 25 µl 0.1 M Sodium Borate Buffer pH=10 and incubating at 40°C for 3 hours. Then the material is lyophilized and dissolved in 85 µl H_2O.

Ligation of C-tags

In each well ligation of double-stranded C-tags were performed as described for A- and B-tags.

Load of position C building blocks (reactants)

Samples to undergo isocyanate addition are redissolved in 8 µl buffer (100mM sodium borate and 100mM sodium phosphate pH 8.0) 1 µl of a specific building block (300 mM in CH_3CN) are added to each well and incubated at 50°C for 16 hours in a in PCR-machine (Eppendorf Mastercycler Gradient).

Samples to undergo sulfonylation were dissolved in 8 µl 100 mM Sodium Borate buffer pH 9. Then, 2 µl specific building block (100 mM in tetrahydrofuran) was then to each well and incubated at 30°C for 16 hours in a PCR-machine.

Samples to undergo acylation were dissolved in 5 µl 200 mM Na-phosphate buffer pH 8.0 or 100 mM Na-Borate pH 9.0 or 100 mM Na-Borate pH 10.0. Then, 4 µl specific building block (100 mM in dimethylsulfoxide) was added to each well. Then 1 µl DMT-MM mix (0.36 M DMT-MM in water and 56 mM Na-phosphate buffer pH 8) was mixed in each well and the sample was incubate at 30° C for 16 hours in a PCR-machine.

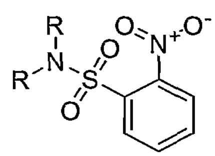
Then an appropriate quenching reagent, e.g. piperidine, is added to each sample to ensure that all reactive species are rendered unreactive. The samples are then pooled and precipitated using 0.05 volumes of 5 M NaCl and 50% isopropanol and washed with cold 70% ethanol

Desphosphorylation

Dephosphorylation is performed as described for A-tags. The sample is then precipitated using 0.05 volumes of 5 M NaCl and 50% isopropanol and washed with cold 70% ethanol.

Ns protection group removal

Secondary amines of position B building blocks (reactants) are protected using Ns:



Scheme 4.2 Ns (2-Nitro-benzenesulfonyl) protection group used for protection of secondary amines.

To remove the Ns protection group, the material is applied to DEAE (which had been washed 2 times with 10 mM Aq. AcOH), then the material on DEAE is washed with water followed by washing with dimethyl formamide. Then the material on DEAE is incubated in a solution of 0.5M mercaptoethanol and 0.25 M DIPEA in dimethyl formamide and incubated for 24 hours at 25°C in an eppendorph thermoshaker at 600 rpm. Then the material on DEAE is washed with 0.3M AcOH in DMF, then twice with DMF and then with water. The Ns-deprotected material is then released from DEAE by adding 70 µl release solution (1.5 M NaCl) and incubating at

25°C for 10 minutes in an eppendorph thermoshaker at 600 rpm. Water is added to the material to a final NaCl concentration of 0.5 M. Then the material is precipitated by adding one volume of isopropanol as described.

Ligation of D-tags

D-tags are ligated as described for A-B-, and C-tags. Then samples were purified using gel-filtration as described and lyophilized.

Load of position D building blocks (reactants)

Samples to undergo isocyanate addition were redissolved in 8 µl buffer (100mM sodium borate and 100mM sodium phosphate pH 8.0) 1 µl of a specific building block (300 mM in CH_3CN) was added to each well and incubated at 50ºC for 16 hours in a in PCR-machine (Eppendorf Mastercycler Gradient). Then, 40 µL of water was added to each sample.

Samples to undergo sulfonylation were dissolved in 8 µl 100 mM Sodium Borate buffer pH 9. 2 µl specific building block (100 mM in tetrahydrofuran) was then to each well and incubated at 30°C for 16 hours in a PCR-machine. Then, 40 µl of water was added to each sample.

Samples to undergo acylation were dissolved in 5 µl 200 mM Na-phosphate buffer pH 8.0 or 100 mM Na-Borate pH 9.0 or 100 mM Na-Borate pH 10.0. Then, 4 µl specific building block (100 mM in dimethylsulfoxide) was added to each well. Then 1 µl DMT-MM mix (0.36 M DMT-MM in water and 56 mM Na-phosphate buffer pH 8) was mixed in each well and the sample was incubate at 30º C for 16 hours in a PCR-machine. Then, 40 µl of water was added to each sample.

Samples to undergo reductive amination were dissolved in 15 µl 200 mM NaOAc buffer pH 5.0 5 ul specific BB was added to each well (200 mM in DMSO) and incubate at 30°C for 1 h. Then 5 µl of freshly prepared 140 mM NaCNBH3 (REA000025; 8.8 mg/ml) in NaOAc buffer pH 5.0 to was added each well and the samples were incubated at 30°C for 16 hours in a PCR-machine (Eppendorf Mastercycler Gradient). Then 25 µl of water was added to each sample.

Samples to undergo nucleophilic aromatic substitution were dissolved in 12 µl 100 mM Borate Buffer pH 9. Then 12 µl specific BB was added to each well (100 mM in

DMSO) and all wells were incubated for 16 hours at 90°C in a PCR-machine (Eppendorf Mastercycler Gradient). Then 40 µl of water was added to each sample.

Then an appropriate quenching reagent, e.g. piperidine, is added to each sample to ensure that all reactive species are rendered unreactive. The samples are then pooled and precipitated using 0.05 volumes of 5 M NaCl and 50% isopropanol and washed with cold 70% ethanol

Fmoc deprotection

Samples are redissolved in water and adjusted to 6% piperidine. Samples are then incubated at 25°C for 30 minutes to remove Fmoc protection groups. Samples are then again precipitated using isopropanol.

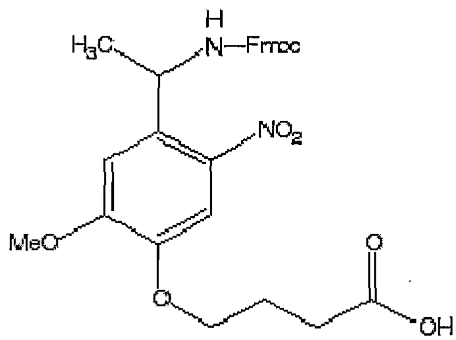
The combined material is redissolved in water and adjusted with polyacrylamide gel electrophoresis loading buffer. The material is electrophoresed and purified by isolating the material corresponding to bifunctional complexes with 4 tags. The single stranded bifunctional complexes are eluted from the gel, precipitated using isopropanol as described, and purified by gel-filtration as described.

Primer extension and affinity selection is the performed as described for examples 1 and 2.

Example 5: Synthesis of bifunctional complexes containing a cleavable linker and release of display molecules

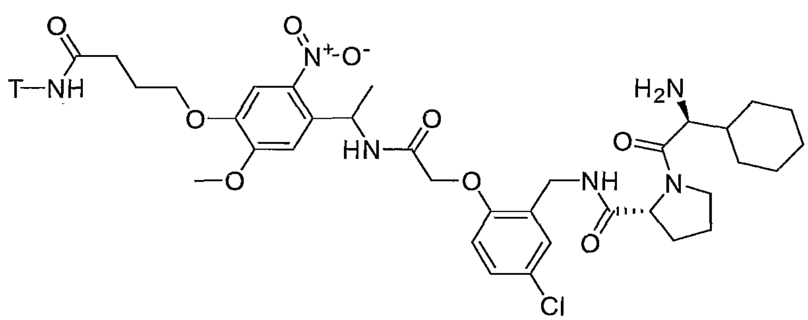
Bifunctional complexes are synthesized from an initial bifunctional complex which contains a chemical reaction site linked with a cleavable linker to a tag. If bifunctional complexes are synthesized in a parallel synthesis fashion it is not necessary to add tags which encode the building blocks (reactants) that are added at the chemical reaction site(s). If bifunctional complexes are synthesized by a split-pool method, tags which encode the different building blocks (reactants) can be added during synthesis as described in examples 1 and 2. Following a split-pool synthesis the bifunctional complexes can then be sorted by employing capture oligos which hybridize to specific codons in the identifier oligonucleotides of the bifunctional complexes.

After synthesis and purification, the cleavable linker is cleaved using appropriate conditions such as electromagnetic radiation, enzymes etc. For example, a cleavable linker such as:

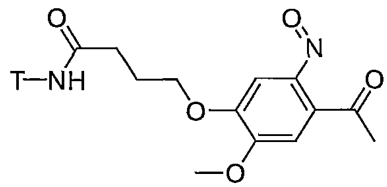


can be cleaved using ultraviolet radiation. The released small molecule can then be used in an assay to determine a property of the display molecule.

The bifunctional complex containing a DNA tag (T):

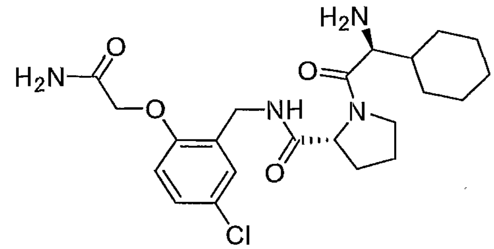


was synthesized employing the chemical reactions (acylation and Fmoc deprotection) as described in example 2. The bifunctional complex was exposed to ultraviolet radiation (omnilux lamp E40, Steinigke Showtechnic Germany) for 120 seconds to release the display molecule:



Tag residual

+



Display Molecule

To determine the Ki of the released display molecule against the protease thrombin, human alpha-thrombin (Heamatologic Technologies Inc.) was diluted in buffer (0.015 units/µl) and the released display molecule was added. Following 5 minutes of incubation at 22°C a chromogenic substrate (Chromogenix catalogue number S-2238) was added and the maximum turnover (Vmax) of the enzyme was determined in a by measuring the change in absorbance at 405 nm using a Versamax reader (Molecular Devices). This was repeated for different concentrations of the released display molecule and different concentrations of substrate. The Vmax values obtained were then fitted using nonlinear regression implemented in the Prism software (Graphpad) to obtain the Ki of the display molecule. A Ki value of 5.2 nM was obtained (95% confidence interval: 0-13 nM).

Example 6. Synthesis and affinity selection of a library encoding on the order of 1.100.000.000 compounds

The first set of building blocks (reactants) were loaded onto a display oligo (see figure 1.2).

The described general procedures were used in the following order:
Position A building blocks (reactants) and A-tags: R1-P1-QC1-V1-T1-QC3-M1-V2-D1-V2-P3-V2-S1-V1

80 position A building blocks (reactants) were used. The building block were trifunctional with one free –COOH reactive group, one Ns-protected amine and one Msec-protected amine.

Position B building blocks (reactants) and B-tags: R1-P1-QC1-V1-T1-QC3-M1-V2-D1-V2-P3-V2-S1-V1

192 position B building blocks (reactants) were used

Position C building blocks (reactants) and C-tags: (R1/R2/R3)-P1-QC1-V1-T1-QC3-M1-V2-D2-V2-P3-V2-S1-V1

88 isocyanate building blocks (reactants) were used
96 sulfonoyl building blocks (reactants) were used
200 acylation building blocks (reactants) were used

Position D building blocks (reactants) and D-tags: (R1/R3/R4/R5)-P1-QC1-V1-T1-QC3-M1-V2-P3-V2-D1-V2

88 aldehyde building blocks (reactants) were used
16 sulfonoyl building blocks (reactants) were used
24 halogenated heteroaromatic building blocks (reactants) were used
64 acylation building blocks (reactants) were used

Example 7: Screening of a library using unspecific elution

Biotinylated Renin was used as the target.

A fraction of the obtained bifunctional complexes was lyophilized and dissolved in 5 µl target buffer (137 mM NaCl, 2.7 mM KCl, 10 mM sodium phosphate, 0.1% Tween-20 , 0.1%BSA). 50 µl streptavidin sepharose (Amersham Biosciences) slurry was washed in 4x 100 µl target buffer and resuspended in 50 µl target buffer. Then biotinylated target was added to the streptavidin sepharose slurry and the slurry was incubated at 15°C with agitation (1400 rpm) for 30 minutes and subsequently washed 4 times with 100 µl target buffer. A 10XL barrier tip (AH diagnostics, Denmark) were prepared by pushing the tip filter approx. 5 mm towards the end of the tip. The tip was placed in a 1 mL pipette tip. The target-loaded streptavidin sepharose was applied to the tip and washed 3 times with 100 µl target buffer by applying vacuum to the bottom end of the tip. The library was applied to the column and allowed to soak in. Then the column was washed 5 times with 100 µl target buffer. Bifunctional complexes were eluted by applying 50 µl 1% SDS in H2O preheated to 60°C for 10 min followed by centrifugation of the column (1000 rcf for 30 seconds). An additional 25 µl PBS was applied to the column and spun through. The eluted material was re-applied to a fresh column. This cycle was repeated 4 times. A 10 µl sample of eluted material was used PCR using the forward and reverse primers 5'-CAAGTCACCAAGAATTCATG and 5'-TCTGGTGGTCTACGTGCTCT. The PCR product was cloned and sequenced using standard methods.

Example 8. Synthesis and affinity selection of a library encoding on the order of 3.5e6 compounds based on a triazine scaffold

The described general procedures were used in the following order:

Position A building blocks (reactants) and A-tags: R1-P1-QC1-V1-T1-QC3-M1-V2-D1-V2-P3-V2-S1-V1

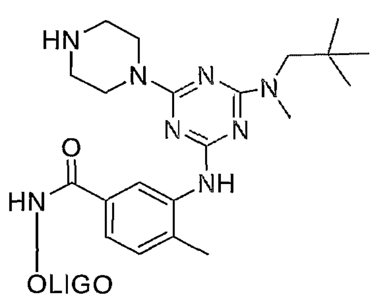
96 position A building blocks (reactants) were used. The building blocks (reactants) were bifunctional with one free –COOH reactive group, one Fmoc-protected amine

The material in all wells were redissolved in 10 µl buffer (100 mM Na-carbonate pH 9.3). 10 µl 1,3,5-trichloro-2,4,6-triazine dissolved to 200 mM in acetone was added to each well and incubated for at 4°C for 1 hour Position B building blocks (reactants) and B-tags: P1-R5-P1-QC1-V1-T1-QC3-M1-V2-D1-V2-P3-V2-S1-V1

192 position B building blocks (reactants) (amines) were used. At the R5 step the material in each well was redissolved in 10 µl 100 mM Na-carbonate pH 9.3 or 10 µl 100 mM Na-phosphate pH 8 and 10 µl building block solution (200 mM in acetone) was added and incubated at 4°C or 25°C for 1 hour or at 30°C for 16 hours.

Position C building blocks (reactants) and C-tags: R5-P1-QC1-V1-T1-QC3-M1-V2-D2-V2-P3-V2

192 position C building blocks (reactants) (amines) were used. At the R5 step the material in each well was redissolved in 10 µl 100 mM Na-borate pH 9.5 and 10 µl building blocks (reactants) (200 mM in DMSO) were added and incubated at 90°C for 16 hours.



Example of a structure generated by this method..

Position D tags: P1-QC1-V1-T1-QC3-M1-V2-P3-V2

No building blocks (reactants) were added at this step. The D-tags were ligated to diversify the bifunctional complexes such that several codon combinations corresponds to the same molecule. 192 different D-tags were used.

The library was screened on kinase p38 using unspecific elution and specific elution using a p38 ligand. The identifiers were amplified and subjected to ultra high-thrughput sequencing. Ligands based on information deduced from the identifier sequences were resynthesized and tested in a p38 kinase assay. 15 ligands with nanomolar IC50 values were identified.

Example 9. <u>Synthesis and affinity selection of a second library designed based on results obtained by synthesis and affinity seelction of a first library.</u>

A library encoding on the order of 110.000.000.000 molecules was synthesized using the method described in example 6. Briefly,

The first set of building blocks (reactants) were loaded onto a display oligo (see figure 1.2).

The described general procedures were used in the following order:
Position A building blocks (reactants) and A-tags: R1-P1-QC1-V1-T1-QC3-M1-V2-D1-V2-P3-V2-S1-V1

576 position A building blocks (reactants) were used. The building block were trifunctional with one free –COOH reactive group, one Ns-protected amine and one Msec-protected amine.

Position B building blocks (reactants) and B-tags: R1-P1-QC1-V1-T1-QC3-M1-V2-D1-V2-P3-V2-S1-V1

576 position B building blocks (reactants) were used

Position C building blocks (reactants) and C-tags: (R1/R2/R3)-P1-QC1-V1-T1-QC3-M1-V2-D2-V2-P3-V2-S1-V1

96 isocyanate building blocks (reactants) were used
96 sulfonoyl building blocks (reactants) were used
384 acylation building blocks (reactants) were used

Position D building blocks (reactants) and D-tags: (R1/R3/R4/R5)-P1-QC1-V1-T1-QC3-M1-V2-P3-V2-D1-V2

96 aldehyde building blocks (reactants) were used

96 sulfonoyl building blocks (reactants) were used
96 halogenated heteroaromatic building blocks (reactants) were used
96 acylation building blocks (reactants) were used
96 isocyanate building blocks (reactants) were used

The library was screened using unspecific elution (example 7), identifiers were amplified and analyzed by ultra high-throughput sequencing. The sequencing revealed that identifiers containing the following tag combinations had been enriched:

A523-B201-C341-D234
A523-B201-C341-D234
A523-B156-C341-D234
A523-B156-C341-D142
A523-B201-C341-D142

(Tags A001-A576, B001-B576, C001-C576, and D001-576 were used for library synthesis at positions A,B,C, and D, respectively).

Ligands corresponding to said enriched identifiers were synthesized according to the method described in example 5. The affinity could not be determined in an affinity assay indicating that the ligands had affinities lower than 10 μM in the assay.

However, a second library was synthesized including the reactants corresponding to the tags in the enriched identifiers. Furthermore, reactants that were analogous in structure or function to said reactants were also used for synthesiz of the second library.

The second library encoded on the order of 110.000.000.000 molecules and was synthesized using the method described in example 6. Briefly,

The first set of building blocks (reactants) were loaded onto a display oligo (see figure 1.2).

The described general procedures were used in the following order:

Position A building blocks (reactants) and A-tags: R1-P1-QC1-V1-T1-QC3-M1-V2-D1-V2-P3-V2-S1-V1

576 position A building blocks (reactants) were used. The building block were trifunctional with one free –COOH reactive group, one Ns-protected amine and one Msec-protected amine.

Position B building blocks (reactants) and B-tags: R1-P1-QC1-V1-T1-QC3-M1-V2-D1-V2-P3-V2-S1-V1

576 position B building blocks (reactants) were used

Position C building blocks (reactants) and C-tags: (R1/R2/R3)-P1-QC1-V1-T1-QC3-M1-V2-D2-V2-P3-V2-S1-V1

96 isocyanate building blocks (reactants) were used

192 sulfonoyl building blocks (reactants) were used

192 acylation building blocks (reactants) were used

Position D building blocks (reactants) and D-tags: (R1/R3/R4/R5)-P1-QC1-V1-T1-QC3-M1-V2-P3-V2-D1-V2

96 aldehyde building blocks (reactants) were used

96 sulfonoyl building blocks (reactants) were used

192 halogenated heteroaromatic building blocks (reactants) were used

96 acylation building blocks (reactants) were used

The library was screened using unspecific elution (example 7), identifiers were amplified and analyzed by ultra high-throughput sequencing. The sequencing revealed that identifiers containing the following tag combinations had been enriched:

A543-B203-C131-D236
A543-B203-C131-D236
A543-B158-C131-D236
A543-B158-C131-D122
A543-B203-C131-D122

Ligands corresponding to said enriched identifiers were synthesized according to the method described in example 5. The affinity of the ligands were determined to be in the 1 nM to 10 μM range.

Claims

1. A method for the synthesis of a bifunctional complex comprising a molecule and a single stranded oligonucleotide identifier attached to the molecule, said method comprising the steps of

   i) providing a display oligonucleotide attached to

      a) one or more chemical reaction site(s) comprising one or more reactive groups and

      b) one or more priming site(s) for enzymatic addition of a tag,

   ii) providing a first reactant comprising one or more chemical entities and one or more reactive groups capable of reacting with

      c) the chemical reaction site(s) of the display oligonucleotide, and/or

      d) one or more reactive groups of at least a first further reactant comprising one or more chemical entities, wherein said first further reactant is provided simultaneously or sequentially in any order with the first reactant,

   iii) providing a first oligonucleotide tag capable of hybridising to part of a first oligonucleotide anti-tag, wherein the first oligonucleotide tag identifies the first reactant and, optionally, the further first reactant,

   iv) providing a first oligonucleotide anti-tag capable of hybridising to at least part of the first oligonucleotide tag provided in step iii) and to at least part of the display oligonucleotide provided in step i),

   v) reacting the first reactant provided in step ii) with c) the one or more chemical reaction site(s) of the display oligonucleotide and/or with d) the one or more reactive groups of the first further reactant comprising one or more chemical entities,

wherein the reaction of complementary reactive groups result in the formation of a covalent bond, and

wherein one or more reactive group reactions of step v) result in the formation of one or more covalent bond(s) between the chemical reaction site(s) of the display oligo and at least one chemical entity of at least one reactant selected from the group consisting of the first reactant and the further first reactant,

vi) hybridising the anti-tag to the display oligonucleotide and to the first oligonucleotide tag,

wherein method steps v) and vi) are simultaneous or sequential in any order,

vii) enzymatically ligating the display oligonucleotide and the first oligonucleotide tag,

viii) providing a second reactant comprising one or more chemical entities and one or more reactive groups capable of reacting with

c) the chemical reaction site(s) of the display oligonucleotide, and/or

d) one or more reactive groups of one or more reactant(s) having reacted in a previous synthesis round, and/or

e) one or more reactive groups of at least a second further reactant comprising one or more chemical entities, wherein said second further reactant is provided simultaneously or sequentially in any order with the second reactant,

ix) providing a second oligonucleotide tag capable of hybridising to part of a second oligonucleotide anti-tag, wherein the second oligonucleotide tag identifies the second reactant and, optionally, the further second reactant,

x) providing a second oligonucleotide anti-tag capable of hybridising to part of the first oligonucleotide tag provided in step iii) and to part of the second oligonucleotide tag provided in step ix),

xi) reacting the second reactant provided in step viii) with c) the chemical reaction site(s) of the display oligonucleotide and/or d) one or more reactive groups of one or more reactant(s) having reacted in a previous synthesis round and/or e) one or more reactive groups of a further second reactant comprising one or more chemical entities,

wherein the reaction of complementary reactive groups result in the formation of a covalent bond, and

wherein one or more reactive group reactions of step xi) result in

f) the formation of one or more covalent bond(s) between the one or more chemical reaction site(s) and at least one chemical entity of at least one reactant selected from the group consisting of the second reactant and the further second reactant, and/or

g) the formation of one or more covalent bond(s) between a reactant having reacted in a previous synthesis round and at least one chemical entity of at least one reactant selected from the group consisting of the second reactant and the further second reactant,

xii) hybridising the anti-tag to the first oligonucleotide tag and the second oligonucleotide tag,

wherein method steps xi) and xii) are simultaneous or sequential in any order,

xiii) enzymatically ligating the first and second oligonucleotide tags in the absence of ligation the first and second anti-tag oligonucleotides, and optionally

xiv) displacing unligated anti-tags from the bifunctional complex comprising a molecule and a single stranded oligonucleotide identifier comprising tags identifying the reactants which participated in the synthesis of the molecule.

2. The method of claim 1, wherein the method of claim 1 is performed in parallel in different reaction compartments, wherein the display oligonucleotide of step i) is provided in each of a plurality of separate reaction compartments and subsequently, wherein, in each of said reaction compartments, the first reactant and optionally also the further first reactant is/are reacted with the one or more chemical reaction site(s), and wherein, in each of said compartments, a first oligonucleotide tag identifying said one or more reactant(s) is added enzymatically to the one or more priming site(s), said reaction(s) of said reactant(s) and said addition(s) of said tag resulting in the formation, in each of said reaction compartments, of different nascent bifunctional complexes.

3. The method of claim 2, wherein said different nascent bifunctional complexes are mixed, and wherein said mixture of different nascent bifunctional complexes is subsequently divided into a plurality of different reaction compartments.

4. The method of claim 3, wherein a different nascent bifunctional complex is provided in each of said plurality of separate reaction compartments and subsequently, in each of said reaction compartments, the second reactant and optionally also the further second reactant is/are reacted with one or more of a chemical reaction site and one or more reactive group(s) of a first reactant and/or further first reactant, and wherein, in each of said compartments, a second oligonucleotide tag identifying said one or more reactant(s) is added enzymatically to the first oligonucleotide tag, said reaction(s) of said reactant(s) and said addition(s) of said tag resulting in the formation, in each of said compartments, of further different nascent bifunctional complexes.

5. The method of claim 4, wherein, in each subsequent round of parallel synthesis, the reactant reaction product of a previous synthesis round reacts with the reactant in a subsequent synthesis round, and wherein a tag added in a previous synthesis

round acts as a substrate for the enzyme which adds a tag in a subsequent synthesis round.

6. The methods of any of claims 1 to 5, wherein the addition of a tag and the reaction of the one or more reactant(s) occur simultaneously.

7. The methods of any of claims 1 to 5, wherein the addition of a tag and the reaction of the one or more reactant(s) occur sequentially in any order.

8. The method of claim 7, wherein a tag is added prior to the reaction of the one or more reactants.

9. The method of claim 7, wherein a tag is added after the reaction of the one or more reactants.

10. The method of any of claims 1 to 9, wherein individual tags differ from each other by at least a single nucleotide substitution.

11. The method of any of claims 1 to 9, wherein individual tags differ from each other by at least 2 nucleotide substitutions.

12. The method of any of claims 10 and 11, wherein individual tags differ from each other by less than 10 nucleotide substitutions.

13. The method of any of claims 1 to 12, wherein the identifier oligonucleotide is amplifiable.

14. The method of any of claims 1 to 13, wherein the display oligonucleotide preferably has a length of from about 3 consecutive nucleotides to about 25 consecutive nucleotides.

15. The method of claim 14, wherein the display oligonucleotide has from 5 to about 20 consecutive nucleotides, for example from 10 to 20 consecutive nucleotides, such as 6 nucleotides, for example 7 nucleotides, such as 8 nucleotides, for example 9 nucleotides, such as 10 nucleotides, for example11 nucleotides, such as 12

nucleotides, for example 13 nucleotides, such as 14 nucleotides, for example 15 nucleotides, such as 16 nucleotides, for example 17 nucleotides, such as 18 nucleotides, for example 19 nucleotides.

16. The method of any of claims 14 and 15, wherein tag(s) preferably have from about 3 consecutive nucleotides to about 25 consecutive nucleotides.

17. The method of claim 16, wherein the tag(s) have from 5 to about 20 consecutive nucleotides, such as 6 nucleotides, for example 7 nucleotides, such as 8 nucleotides, for example 9 nucleotides, such as 10 nucleotides, for example11 nucleotides, such as 12 nucleotides, for example 13 nucleotides, such as 14 nucleotides, for example 15 nucleotides, such as 16 nucleotides, for example 17 nucleotides, such as 18 nucleotides, for example 19 nucleotides.

18. The method of any of claims 14 to 17, wherein anti-tag(s) preferably have from about 3 consecutive nucleotides to about 25 consecutive nucleotides.

19. The method of claim 19, wherein anti-tags preferably have from 5 to about 20 consecutive nucleotides, such as 6 nucleotides, for example 7 nucleotides, such as 8 nucleotides, for example 9 nucleotides, such as 10 nucleotides, for example11 nucleotides, such as 12 nucleotides, for example 13 nucleotides, such as 14 nucleotides, for example 15 nucleotides, such as 16 nucleotides, for example 17 nucleotides, such as 18 nucleotides, for example 19 nucleotides.

20. The method of any of claims 14 to 19, wherein single-stranded over-hangs resulting from hybridisation of tags and anti-tags preferably have a length of from about 3 consecutive nucleotides to about 25 consecutive nucleotides.

21. The method of claim 20, wherein the single-stranded over-hangs preferably have from 3 to about 20 consecutive nucleotides, such as from 4 to about 20 consecutive nucleltides, for example from 5 to about 20 consecutive nucleotides, such as from 3 to 10 consecutive nucleotides, such as from 4 to about 10 consecutive nucleltides, for example from 5 to about 10 consecutive nucleotides, such as from 3 to 8 consecutive nucleotides, such as from 4 to about 8 consecutive nucleltides, for example from 5 to about 8 consecutive nucleotides, such as 3

nucleotides, for example 4 nucleotides, such as 5 nucleotides, for example 6 nucleotides, for example 7 nucleotides, such as 8 nucleotides, for example 9 nucleotides, such as 10 nucleotides, for example11 nucleotides, such as 12 nucleotides, for example 13 nucleotides, such as 14 nucleotides, for example 15 nucleotides, such as 16 nucleotides, for example 17 nucleotides, such as 18 nucleotides, for example 19 nucleotides.

22. The method of any of claims 1 to 21, wherein the identifier oligonucleotide resulting from tag ligation(s) has a length of from 6 to about 200 consecutive nucleotides.

23. The method of any of claims 1 to 21, wherein the identifier oligonucleotide resulting from tag ligation(s) has a length of from 10 to about 100 consecutive nucleotides.

24. The method of any of claims 1 to 23, wherein the identifier oligonucleotide comprises a string of consecutive nucleotides comprising from 2 to 10 tags, for example from 3 to 10 tags, such as from 4 to 10 tags, for example from 5 to 10 tags, such as from 6 to 10 tags, for example from 7 to 10 tags, such as from 8 to 10 tags, for example from 2 to 9 tags, such as from 2 to 8 tags, for example from 2 to 7 tags, such as from 2 to 6 tags, for example from 2 to 5 tags, such as from 2 to 4 tags, for example 2 or 3 tags, such as from 3 to 9 tags, such as from 3 to 8 tags, for example from 3 to 7 tags, such as from 3 to 6 tags, for example from 3 to 5 tags, such as from 3 to 4 tags, for example from 4 to 9 tags, such as from 4 to 8 tags, for example from 4 to 7 tags, such as from 4 to 6 tags, for example from 4 to 5 tags, such as from 5 to 9 tags, such as from 5 to 8 tags, for example from 5 to 7 tags, such as 5 or 6 tags, for example 2, 3, 4 or 5 tags, such as 6, 7 or 8 tags, for example 9 or 10 tags.

25. The method of any of claims 1 to 24, wherein the display oligonucleotide comprises or essentially consists of nucleotides selected from the group consisting of deoxyribonucleic acids (DNA), ribonucleic acids (RNA), peptide nucleic acids (PNA), locked nucleic acids (LNA), and morpholinos sequences, including any analog or derivative thereof.

26. The method of any of claims 1 to 25, wherein one or more oligonucleotide tags comprise or essentially consist of nucleotides selected from the group consisting of

deoxyribonucleic acids (DNA), ribonucleic acids (RNA), peptide nucleic acids (PNA), locked nucleic acids (LNA), and morpholinos sequences, including any analog or derivative thereof.

27. The method of any of claims 1 to 26, wherein one or more anti-tag oligonucleotides comprise or essentially consist of nucleotides selected from the group consisting of deoxyribonucleic acids (DNA), ribonucleic acids (RNA), peptide nucleic acids (PNA), locked nucleic acids (LNA), and morpholinos sequences, including any analog or derivative thereof.

28. The method of any of claims 25 to 27, wherein the nucleotide analogs are selected from nucleotides wherein the nucleobase part of the nucleotide comprises a heterocyclic analog and tautomers thereof, selected from the group consisting of xanthine, diaminopurine, 8-oxo-N^6-methyladenine, 7-deazaxanthine, 7-deazaguanine, N^4,N^4-ethanocytosin, N^6,N^6-ethano-2,6-diamino-purine, 5-methylcytosine, 5-(C^3-C^6)-alkynylcytosine, 5-fluorouracil, 5-bromouracil, pseudoisocytosine, 2-hydroxy-5-methyl-4-triazolopyridine, isocytosine, isoguanine and inosine.

29. The method of any of claims 25 to 28, wherein the backbone moiety of the display oligonucleotide and/or the oligonucleotide tags and/or the anti-tag oligonucleotides comprises or consists of a sugar moiety and an internucleoside linker connecting the nucleobase part of neighboring nucleotides.

30. The method of claim 29, wherein the internucleoside linker connects the 3' end of preceding nucleotide to a 5' end of a succeeding nucleotide.

31. The method of claim 30, wherein the sugar moiety is a pentose.

32. The method of claim 31, wherein the pentose is a ribose or 2'-deoxyribose.

33. The method of claim 31, wherein the sugar moiety is selected from the group consisting of 2'-deoxyribose, 2'-O-methyl-ribose, 2'-flour-ribose and 2'-4'-O-methylene-ribose (LNA).

34. The method of any of claims 32 and 33, wherein the nucleobase part of the nucleotide is attached to the 1' position of the pentose.

35. The method of any of claims 29 to 34, wherein the internucleoside linker comprises one or more bonds selected from the group consisting of a phospodiester bond, a phosphorothioate bond, a methylphosphonate bond, a phosphoramidate bond, a phosphotriester bond and a phosphodithioate bond.

36. The method of any of claims 25 to 27, wherein the nucleobase part of one or more display oligonucleotide(s) and/or one or more oligonucleotide tag(s) and/or one or more anti-tag oligonucleotides are selected from naturally occurring nucleosides selected from deoxyadenosine, deoxyguanosine, deoxythymidine, adenosine, guanosine, uridine, cytidine, and inosine, wherein said nucleosides are connected by an internucleoside linker selected from the group consisting of a phospodiester bond, a phosphorothioate bond, a methylphosphonate bond, a phosphoramidate bond, a phosphotriester bond and a phosphodithioate bond

37. The method of claim 36, wherein the internucleoside linker is a phosphodiester bond.

38. The method of any of claims 1 to 37, wherein end-positioned nucleotides of anti-tags comprises no reactive group(s), such as a 5'-P and/or a 3'-OH reactive group(s), capable of being linked by an enzyme comprising ligase activity.

39. The method of any of claims 1 to 38, wherein the one or more priming site(s) of the display oligonucleotide comprises a 3'-OH or 5'-phosphate group, or a functional derivative of such a group, capable of being linked by an enzyme comprising ligase activity.

40. The method of any of claims 1 to 39, wherein molecule decoding or reactant identification is performed by sequencing all or some of the nucleotides of each tag of the identifier oligonucleotide.

41. The method of any of claims 1 to 40, wherein the enzyme comprising ligase activity is selected from Taq DNA ligase, T4 DNA ligase, T4 RNA ligase, T7 DNA ligase, and *E. coli* DNA ligase.

42. The method of claim 41, wherein the enzyme is Taq DNA ligase.

43. The method of any of claims 1 to 42, wherein the one or more chemical reaction site(s) of the display oligonucleotide each comprising one or more reactive groups react with one or more reactants each comprising one or more reactive groups, wherein the chemical reaction sites can the same or different chemical reaction sites, wherein the reactive groups can be the same or different reactive groups, and wherein the reactants can be the same or different reactants.

44. The method of claim 43, wherein the display oligonucleotide comprises one chemical reaction site.

45. The method of claim 44, wherein the chemical reaction site comprises more than one reactive groups.

46. The method of claim 44, wherein the chemical reaction site comprises a single reactive group.

47. The method of claim 43, wherein the display oligonucleotide comprises more than one chemical reaction site.

48. The method of claim 47, wherein the more than one chemical reaction site each comprises more reactive groups.

49. The method of claim 47, wherein the more than one chemical reaction site each comprises a single reactive group.

50. The method of any of claims 44 to 49, wherein each chemical reaction site reactive group is reacted with one or more reactants each comprising one or more reactive groups.

51. The method of claim 50, each chemical reaction site reactive group is reacted with one reactant only in the form of a first reactant.

52. The method of claim 50, wherein each chemical reaction site reactive group is reacted with more than one reactant.

53. The method of any of claims 51 and 52, wherein one reactive group of each reactant is reacted with a chemical reactive site reactive group.

54. The method of any of claims 51 and 52, wherein more then one reactive group of each reactant is reacted with a chemical reactive site reactive group.

55. The method of claim 52, wherein one reactive group of one reactant reacts with a chemical reaction site reactive group and wherein more than one reactive group of another reactant reacts with the same or a different chemical reaction site reactive group.

56. The method of claim 55, wherein one reactive group of one reactant reacts with one chemical reaction site reactive group and wherein more than one reactive group of another reactant reacts with a different chemical reaction site reactive group.

57. The method of any of claims 43 to 56, wherein the more than one reactive groups are selected from the group consisting of 2 reactive groups, 3 reactive groups, 4 reactive groups, 5 reactive groups, 6 reactive groups, 7 reactive groups, 8 reactive groups, 9 reactive groups and 10 reactive groups, which can be the same or different reactive groups.

58. The method of any of claims 43 to 57, wherein the more than one reactants are selected from the group consisting of 2 reactants, 3 reactants, 4 reactants, 5 reactants, 6 reactants, 7 reactants, 8 reactants, 9 reactants and 10 reactants, which can be the same or different reactants.

59. The method of any of claims 1 to 58, wherein the reactive groups involved in the synthesis of a molecule are selected from carboxylic acids, alcohols, thiols,

aldehydes, ketones, amides, imides, amines, azo, diazo, azido, hydrazines, carbamates, esters, thioesters, cyanides, ethers, isocyanates, isothiocyanates, sulfides, nitriles, nitrites, nitrates, nitro, peroxides, phosphates, thiophosphates, sulfides, epoxides, anhydrides, halides, acid halides, organometallics, nitrides, phosphides, carbides, and silicides.

60. The method of any of claims 1 to 59, wherein the reaction of the chemical reaction site and a reactant, or the reaction of different reactants, results in the formation of at least one bond selected from the group consisting of peptide bonds, sulfonamide bonds, ester bonds, saccharide bonds, carbamate bonds, carbonate bonds, urea bonds, phosphonate bonds, urethane bonds, azatide bonds, peptoid bonds, ether bonds, ethoxy bonds, thioether bonds, single carbon bonds, double carbon bonds, triple carbon bonds, disulfide bonds, sulfide bonds, phosphodiester bonds, oxime bonds, imine bonds, imide bonds, including any combination thereof.

61. The method of any of claims 1 to 59, wherein the reaction of the chemical reaction site and a reactant, or the reaction of different reactants, results in the formation of at least one bond selected from the group consisting of -NHN(R)CO- ; -NHB(R)CO- ; -NHC(RR')CO- ; -NHC(=CHR)CO- ; $-NHC_6H_4CO-$; $-NHCH_2CHRCO-$; $-NHCHRCH_2CO-$; $-COCH_2-$; -COS- ; -CONR- ; -COO- ; -CSNH- ; $-CH_2NH-$; $-CH_2CH_2-$; $-CH_2S-$; $-CH_2SO-$; $-CH_2SO_2-$; $-CH(CH_3)S-$; -CH=CH- ; -NHCO- ; -NHCONH- ; -CONHO- ; $-C(=CH_2)CH_2-$; $-PO_2^-NH-$; $-PO_2^-CH_2-$; $-PO_2^-CH_2N^+-$; $-SO_2NH^--$; and lactams.

62. The method of any of claims 1 to 61, wherein complementary reactive groups of the chemical reaction site and/or the reactive group(s) of one or more reactants reacting with each other and/or with the chemical reaction site are selected from the group consisting of

a) activated carboxyl groups, reactive sulfonyl groups and reactive phosphonyl groups, or a combination thereof, and complementary primary or secondary amino groups; wherein the complementary reactive groups react under suitable conditions to form amide, sulfonamide and/or phosphonamidate bonds;

b) epoxide groups and complementary primary and/or secondary amino groups;

wherein a reactant comprising one or more epoxide reactive group(s) reacts with one or more amine-group(s) of a complementary reactant under suitable conditions to form one or more carbon-nitrogen bond(s);

c) aziridine groups and complementary primary or secondary amino groups; wherein under suitable conditions, a reactant comprising one or more aziridine-group(s) reacts with one or more amine-group(s) of a complementary reactant to form one or more carbon-nitrogen bond(s);

d) isocyanate groups and complementary primary or secondary amino groups, wherein a reactant comprising one or more isocyanate-group(s) reacts with one or more amino-group(s) of a complementary reactant under suitable conditions to form one or more carbon-nitrogen bond(s);

e) isocyanate groups and complementary hydroxyl groups; wherein a reactant comprising one or more isocyanate-group(s) reacts with a complementary reactant comprising one or more hydroxyl-groups under suitable conditions to form one or more carbon-oxygen bond(s);

f) amino groups and complementary carbonyl groups; wherein a reactant comprising one or more amino groups reacts with a complementary reactant comprising one or more carbonyl-group(s), such as aldehyde and/or ketone group(s); wherein the amines react with such groups via reductive amination to form e.g. a carbon-nitrogen bond;

g) phosphorous ylide groups and complementary aldehyde and/or ketone groups; wherein a reactant comprising a phosphorus-ylide-group reacts with an aldehyde and/or a ketone-group of a complementary reactant under suitable conditions to form e.g. a carbon-carbon double bond;

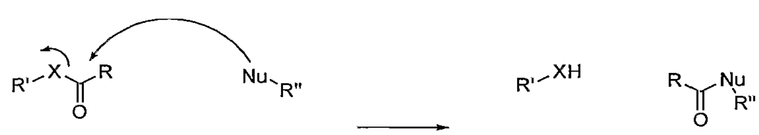
h) complementary reactive groups reacting via cycloaddition to form a cyclic structure; such as the reaction of alkynes and organic azides, which react under suitable conditions to form a triazole ring structure;

i) alkyl halide groups and one or more nucleophile group(s), such as amino groups,

hydroxyl groups and carboxyl group; wherein such groups react under suitable conditions to form a carbon-nitrogen bond (alkyl halide plus amine) or carbon oxygen bond (alkyl halide plus hydroxyl or carboxyl group); and

j) halogenated heteroaromatic groups and one or more nucleophile group(s), wherein the reactants react under suitable conditions via aromatic nucleophilic substitution; wherein halogenated heteroaromatic groups are optionally selected from chlorinated pyrimidines, triazines and purines, which react with nucleophiles, such as amines, under mild conditions in aqueous solution.

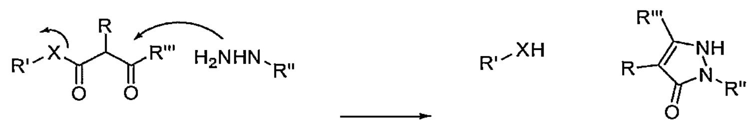
63. The method of any of claims 1 to 61, wherein at least one complementary reactive group reaction is a nucleophilic substitution using activation of electrophiles as illustrated herein below



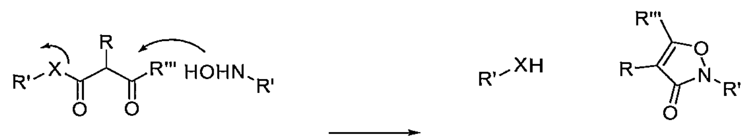
X = O , S Nu = Oxygen- , Nitrogen- , Sulfur- and Carbon Nucleophiles

64. The method of any of claims 1 to 61, wherein at least one complementary reactive group reaction is an acylation resulting in amide bond formation by reaction of amines with activated esters as illustrated herein below

65. The method of any of claims 1 to 61, wherein at least one complementary reactive group reaction is an acylation resulting in a pyrazolone formation by reaction of hydrazines with β–ketoesters as illustrated herein below

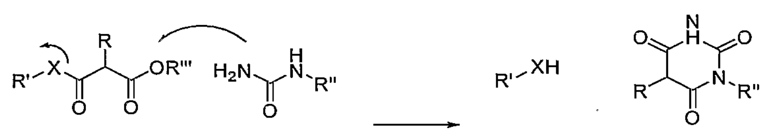


66. The method of any of claims 1 to 61, wherein at least one complementary reactive group reaction is an acylation resulting in isoxazolone formation by reaction of hydroxylamines with β–ketoesters as illustrated herein below

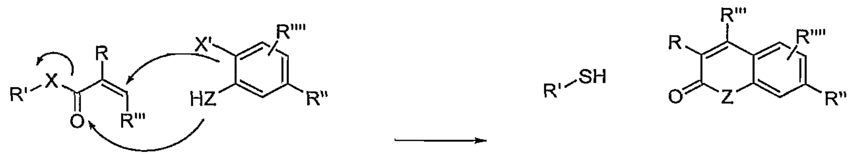


67. The method of any of claims 1 to 61, wherein at least one complementary reactive group reaction is an acylation resulting in pyrimidine formation by reaction of thioureas with β–Ketoesters as illustrated herein below

68. The method of any of claims 1 to 61, wherein at least one complementary reactive group reaction is an acylation resulting in pyrimidine formation by reaction of ureas with malonates as illustrated herein below

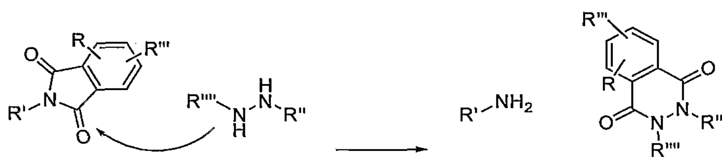


69. The method of any of claims 1 to 61, wherein at least one complementary reactive group reaction is an acylation resulting in coumarine or quinolinon formation by a Heck reaction followed by a nucleophilic substitution as illustrated herein below

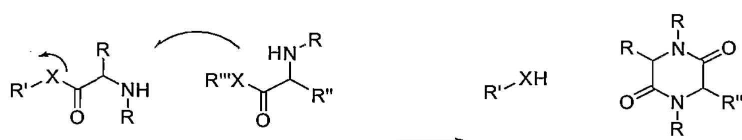


X = O,S X' = Halogen, OTf, OMs Z = O, NH

70. The method of any of claims 1 to 61, wherein at least one complementary reactive group reaction is an acylation resulting in phthalhydrazide formation by reaction of hydrazines and phthalimides as illustrated herein below

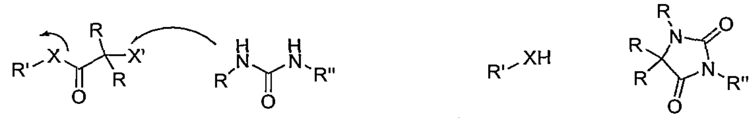


71. The method of any of claims 1 to 61, wherein at least one complementary reactive group reaction is an acylation resulting in diketopiperazine formation by reaction of amino acid esters illustrated by



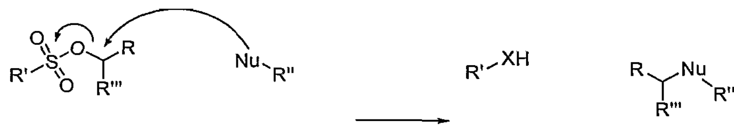
X = O, S R' = H, R

72. The method of any of claims 1 to 61, wherein at least one complementary reactive group reaction is an acylation resulting in hydantoin formation by reaction of urea and α-substituted esters illustrated by



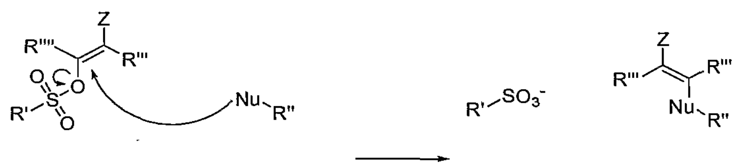
X = O, S X' = Hal, OTos, OMs, etc.

73. The method of any of claims 1 to 61, wherein at least one complementary reactive group reaction is an alkylation based on a reaction of sulfonates with nucleofiles as illustrated herein below



Nu = Oxygen- , Nitrogen- , Sulfur- and Carbon Nucleophiles

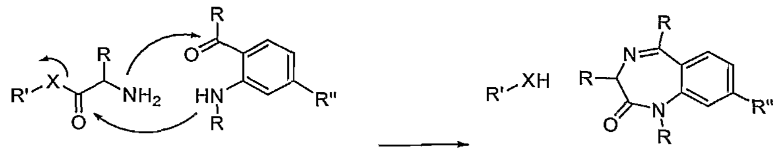
74. The method of any of claims 1 to 61, wherein at least one complementary reactive group reaction is a reaction of vinylating monomers as illustrated herein below



Z = CN, COOR, COR, NO_2, SO_2R, S(=O)R, SO_2NR_2, F
Nu = Oxygen- , Nitrogen- , Sulfur- and Carbon Nucleophiles

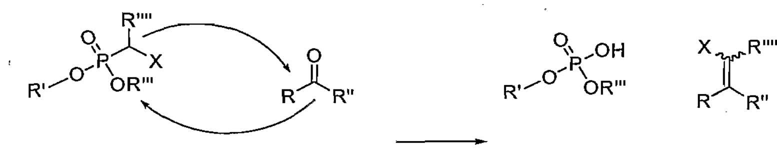
75. The method of any of claims 1 to 61, wherein at least one complementary reactive group reaction is a disulfide formation by reaction of pyridyl disulfide with a mercaptane illustrated by

76. The method of any of claims 1 to 61, wherein at least one complementary reactive group reaction is a benzodiazepinone formation by reaction of amino acid esters and amino ketones illustrated by



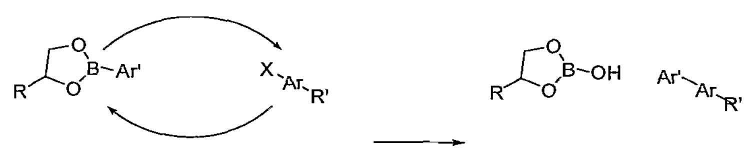
X = O, S

77. The method of any of claims 1 to 61, wherein at least one complementary reactive group reaction is a an addition over carbon-hetero multiple bonds wherein a substituted alkene bond is obtained by reaction of phosphonates with aldehydes or ketones illustrated by



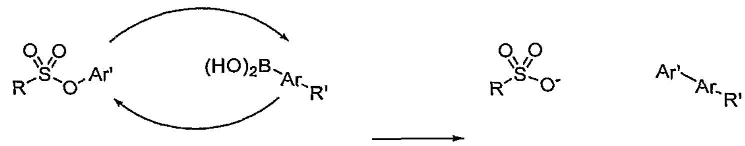
X = EWG

78. The method of any of claims 1 to 61, wherein at least one complementary reactive group reaction is a transition metal catalysed reaction, such as reactions resulting in biaryl formation by reaction of boronates with aryls or heteroaryls illustrated by

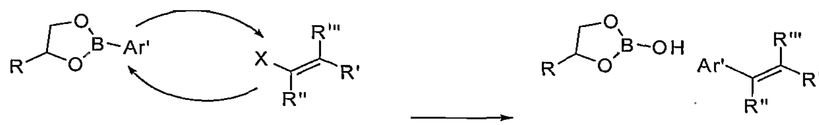


X = Halogen, OMs, OTf, OTos, etc

79. The method of any of claims 1 to 61, wherein at least one complementary reactive group reaction results in a biaryl formation by the reaction of boronates with aryls or heteroaryls illustrated by

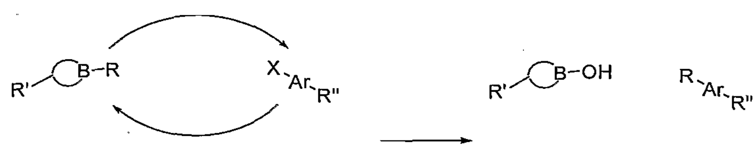


80. The method of any of claims 1 to 61, wherein at least one complementary reactive group reaction results in vinylarene formation by a reaction of alkenes with aryls or heteroaryls illustrated by



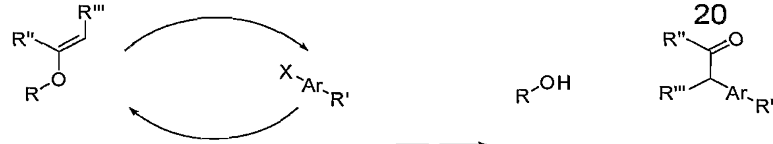
X = Halogen, OMs, OTf, OTos, etc

81. The method of any of claims 1 to 61, wherein at least one complementary reactive group reaction results in a alkylation of arenes or hetarens by a reaction with alkyl boronates illustrated by



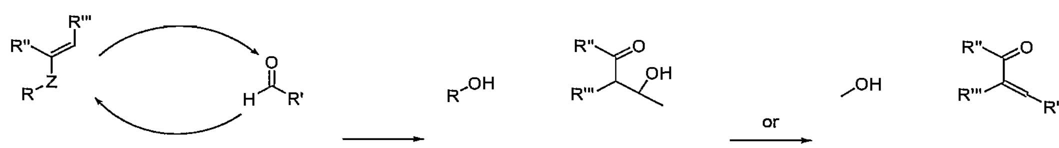
X = Halogen, OMs, OTf, OTos, etc

82. The method of any of claims 1 to 61, wherein at least one complementary reactive group reaction results in alkylation of arenas/hetarenes by reaction with enolethers illustrated by



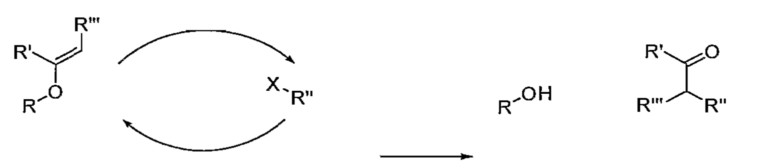
X = Halogen, OMs, OTf, OTos, etc

83. The method of any of claims 1 to 61, wherein at least one complementary reactive group reaction results in a nucleophilic substitution using activation of nucleophiles, such as alkylation of aldehydes with enolethers or enamines illustrated by



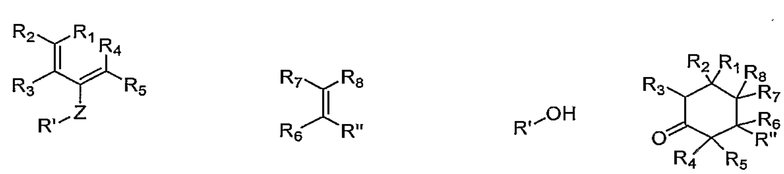
Z = NR, O; X = Halogen, OMs, OTf, OTos, etc

84. The method of any of claims 1 to 61, wherein at least one complementary reactive group reaction results in alkylation of aliphatic halides or tosylates with enolethers or enamines illustrated by



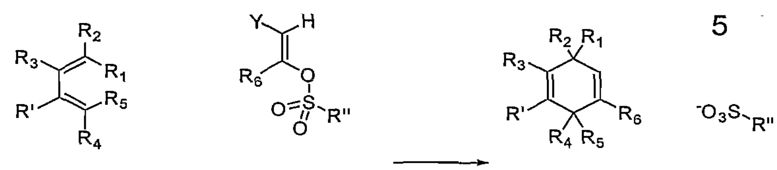
X = Halogen, OMs, OTf, OTos, etc

85. The method of any of claims 1 to 61, wherein at least one complementary reactive group reaction results in a cycloaddition, such as [2+4] cycloadditions illustrated by



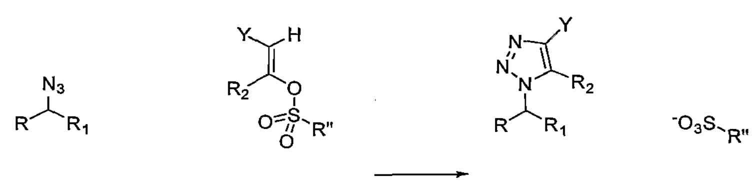
Z = O, NR

86. The method of any of claims 1 to 61, wherein at least one complementary reactive group reaction results in a cycloaddition, such as [2+4] cycloadditions illustrated by



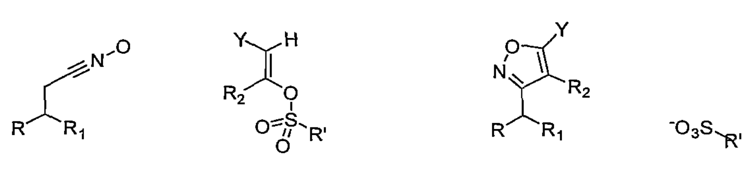
Y, CN, COOR, COR, NO_2, SO_2R, S(=O)R, SO_2NR_2, F

87. The method of any of claims 1 to 61, wherein at least one complementary reactive group reaction results in a cycloaddition, such as [3+2] cycloaddition illustrated by



Y, CN, COOR, COR, NO_2, SO_2R, S(=O)R, SO_2NR_2, F

88. The method of any of claims 1 to 61, wherein at least one complementary reactive group reaction results in a cycloaddition, such as [3+2] cycloaddition illustrated by



Y, CN, COOR, COR, NO_2, SO_2R, S(=O)R, SO_2NR_2, F

89. The method of any of claims 1 to 88, wherein the chemical reaction site comprises a scaffold comprising one or more reactive groups.

90. The method of claim 89, wherein the scaffold reactive groups are selected from carboxylic acids, alcohols, thiols, aldehydes, ketones, amides, imides, amines, azo, diazo, azido, hydrazines, carbamates, esters, thioesters, cyanides, ethers, isocyanates, isothiocyanates, sulfides, nitriles, nitrites, nitrates, nitro, peroxides, phosphates, thiophosphates, sulfides, epoxides, anhydrides, halides, acid halides, organometallics, nitrides, phosphides, carbides, and silicides.

91. The method of claim 89, wherein scaffold comprises a scaffold moiety selected from the group consisting of quinazoline, tricyclic quinazoline, purine, pyrimidine, phenylamine-pyrimidine, phthalazine, benzylidene malononitrile, amino acid, tertiary amine, peptide, lactam, sultam, lactone, pyrrole, pyrrolidine, pyrrolinone, oxazole, isoxazole, oxazoline, isoxazoline, oxazolinone, isoxazolinone, thiazole, thiozolidinone, hydantoin, pyrazole, pyrazoline, pyrazolone, imidazole, imidazolidine, imidazolone, triazole, thiadiazole, oxadiazole, furan, benzoffuran, isobenzofuran, dihydrobenzofuran, dihydroisobenzofuran, indole, indoline, benzoxazole, oxindole, indolizine, benzimidazole, benzimidazolone, pyridine, piperidine, piperidinone, pyrimidinone, piperazine, piperazinone, diketopiperazine, metathiazanone, morpholine, thiomorpholine, phenol, dihydropyran, quinoline, isoquinoline, quinolinone, isoquinolinone, quinolone, quinazolinone, quinoxalinone, benzopiperazinone, benzodiazepine, quinazolinedione, benzazepine, azepine, tropane, and coumarine.

92. The method of any of claims 1 to 91, wherein the molecule is a branched or cyclical molecule.

93. The method of claim 92, wherein the molecule is cyclical and comprises a ring system selected from a single ring system and a fused ring system.

94. The method of claim 93, wherein one or more heteroatoms are present in either the single ring system or in the fused ring system.

95. The method of claim 93, wherein the single ring system is not directly bonded at more than one ring atom to another closed ring, and wherein the fused ring system is directly bonded at more than one ring atom to another closed ring.

96. The method of any of claims 93 to 95, wherein the single ring system is selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl, and heteroaryl each having from about three to about eight, or from about four to about six ring atoms.

97. The method of any of claims 93 to 95, where the fused ring system is selected from aryl and a cyclyl ring system, wherein about six or less, about five or less, about four or less, about three or less, or about two rings are fused.

98. The method of claim 97, wherein each ring system is independently selected from the group consisting of aryl, heteroaryl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl, wherein each of said ring systems can independently be substituted or unsubstituted, such as having from about four to about ten, for example from about four to about thirteen, or from about four to about fourteen ring atoms.

99. The method of claim 94, wherein the one or more heteroatoms are selected from the group consisting of N, O, S, and P, including any oxidized form of nitrogen, sulfur, and phosphorus and the quaternized form of any basic nitrogen.

100. The method of claim 94, wherein the one or more heteroatoms are selected from the group consisting of N, O, or S, including any oxidized form of nitrogen, sulfur, and phosphorus and the quaternized form of any basic nitrogen.

101. The method of any of claims 96 and 97, wherein aryl is an aromatic ring structure having about six ring carbon atoms.

102. The method of claim 101, wherein the aryl is a fused aryl, said fused aryl comprising from about two to about three aromatic rings each having from about six to about ten, such as from about six to about thirteen, for example from about six to about fourteen ring carbon atoms.

103. The method of claim 101, wherein the aryl is a fused heteroaryl, said fused heteroaryl comprising from about two to about three aromatic rings each having from about six to about ten, such as from about six to about thirteen, for example from about six to about fourteen ring carbon atoms.

104. The method of claim 97, wherein the cyclyl ring system comprises a fused cycloalkyl comprising from about two to about three cycloalkyl rings each having from about four to about ten, such as from about four to about thirteen, for example from about four to about fourteen ring carbon atoms.

105. The method of claim 104, wherein the cycloalkyl is a lower cycloalkyl having cycloalkyl groups having from about three to about six ring members.

106. The method of claim 97, wherein the cyclyl ring system comprises a fused heterocycloalkyl comprising from about two to about three heterocycloalkyl rings, wherein at least one of said rings is a heterocycloalkyl having from about four to about ten, such as from about four to about thirteen, for example from about four to about fourteen ring atoms, wherein the heterocycloalkyl is a cycloalkyl comprising one or more heteroatoms in place of a ring carbon atom, said heteroatoms being selected from the group consisting of N, O, S, and P, including any oxidized form of nitrogen, sulfur, and phosphorus and the quaternized form of any basic nitrogen.

107. The method of claim 106, wherein the heterocycloalkyl is a lower heterocycloalkyl having cycloalkyl groups having from about three to about six ring members.

108. The method of any of claims 104 to 107, wherein the cycloalkyl is a heterocycloalkenyl comprising one or more heteroatoms in place of a ring carbon atom.

109. The method of claim 108, wherein the cycloalkyl is a lower heterocycloalkenyl having from about three to about six ring members.

110. The method of claim 98, wherein the heteroaryl is a fused ring system, wherein each ring system has about three, about five, about six, about seven, or

about eight ring atoms, and further optionally comprises one or more heteroatoms, wherein one or more heteroatoms are present in at least one of said ring systems.

111. The method of claim 98, wherein the heteroaryl is a lower heteroaryl and has from about three, such as about five, for example about six ring members.

112. The method of any of the previous claims, wherein the molecule is synthesised by one or more reactions selected from the group consisting of amine acylation, reductive alkylation, aromatic reduction, aromatic acylation, aromatic cyclization, aryl-aryl coupling, [3+2] cycloaddition, Mitsunobu reaction, nucleophilic aromatic substitution, sulfonylation, aromatic halide displacement, Michael addition, Wittig reaction, Knoevenagel condensation, reductive amination, Heck reaction, Stille reaction, Suzuki reaction, Aldol condensation, Claisen condensation, amino acid coupling, amide bond formation, acetal formation, Diels-Alder reaction, [2+2] cycloaddition, enamine formation, esterification, Friedel Crafts reaction, glycosylation, Grignard reaction, Homer-Emmons reaction, hydrolysis, imine formation, metathesis reaction, nucleophilic substitution, oxidation, Pictet-Spengler reaction, Sonogashira reaction, thiazolidine formation, thiourea formation and urea formation.

113. The method of any of claims 1 to 112, wherein the one or more chemical reaction site(s) are covalently linked to the one or more priming site(s).

114. The method of claim 113, wherein the covalent linker comprises a selectively cleavable linker.

115. The method of claim 114, wherein the selectively cleavable linker is cleaved and the display molecule is detached from the identifier oligonucleotide of the bifunctional complex.

116. A method for the synthesis of a plurality of different bifunctional complexes, said method comprising the steps of

i) providing a plurality of display oligonucleotides each attached to

a) one or more chemical reaction site(s) comprising one or more reactive groups and

b) one or more priming site(s) for enzymatic addition of a tag,

ii) providing a plurality of first reactants each comprising one or more chemical entities and one or more reactive groups, each first reactant being capable of reacting with

c) the one or more chemical reaction site(s) of the display oligonucleotide, and/or

d) one or more reactive groups of a first further reactant comprising one or more chemical entities, wherein said first further reactant is provided simultaneously or sequentially in any order with the first reactant,

iii) providing a plurality of first oligonucleotide tags each capable of hybridising to part of a first oligonucleotide anti-tag, wherein each first oligonucleotide tag identifies a first reactant and, optionally, a further first reactant,

iv) providing a plurality of first oligonucleotide anti-tags each capable of hybridising to at least part of a first oligonucleotide tag provided in step iii) and to at least part of a display oligonucleotide provided in step i),

v) reacting each of the first reactants provided in step ii) with c) the one or more chemical reaction site(s) of the display oligonucleotides and/or with d) the one or more reactive groups of a first further reactant comprising one or more chemical entities,

wherein the reaction of complementary reactive groups result in the formation of a covalent bond, and

wherein one or more reactive group reactions of step v) result in the formation of one or more covalent bond(s) between the one or more chemical reaction site(s) of the display oligonucleotides and at least one

chemical entity of at least one reactant selected from the group consisting of a first reactant and a further first reactant,

vi) hybridising anti-tags to display oligonucleotides and to first oligonucleotide tags,

wherein method steps v) and vi) are simultaneous or sequential in any order,

vii) enzymatically ligating display oligonucleotides and first oligonucleotide tags,

viii) dividing the plurality of nascent bifunctional complexes obtained in step vii) into a plurality of different compartments,

ix) providing in each different compartment a plurality of different second reactants each comprising one or more chemical entities and one or more reactive groups capable of reacting with

c) the one or more chemical reaction site(s) of each of the display oligonucleotides, and/or

d) one or more reactive groups of one or more reactant(s) having reacted in a previous synthesis round, and/or

e) one or more reactive groups of a second further reactant comprising one or more chemical entities, wherein said second further reactants are provided simultaneously or sequentially in any order with the second reactants,

x) providing in each different compartment a plurality of second oligonucleotide tags each capable of hybridising to part of a second oligonucleotide anti-tag, wherein different second oligonucleotide tags are provided in each different compartment, and wherein each different second oligonucleotide identifies a different second reactant and, optionally, a further second reactant which

may be the same or a different further second reactant in each different compartment,

xi) providing in each different compartment a plurality of second oligonucleotide anti-tags capable of hybridising to part of a first oligonucleotide tag provided in step iii) and to part of a second oligonucleotide tag provided in step x),

xii) reacting in each different compartment each of the different second reactants provided in step ix) with c) the one or more chemical reaction site(s) of a display oligonucleotide and/or d) one or more reactive groups of one or more reactant(s) having reacted in a previous synthesis round and/or e) one or more reactive groups of a further second reactant comprising one or more chemical entities,

wherein said one or more reactions result in the formation of different bifunctional complexes in each different compartment,

wherein the reaction of complementary reactive groups result in the formation of a covalent bond, and

wherein one or more reactive group reactions of step xii) result in

f) the formation of one or more covalent bond(s) between the one or more chemical reaction site(s) and at least one chemical entity of at least one reactant selected from the group consisting of second reactants and further second reactants, and/or

g) the formation of one or more covalent bond(s) between a reactant having reacted in a previous synthesis round and at least one chemical entity of at least one reactant selected from the group consisting of second reactants and further second reactants,

xiii) hybridising anti-tags to first oligonucleotide tags and second oligonucleotide tags in each different compartment,

wherein method steps xii) and xiii) are simultaneous or sequential in any order,

xiv) enzymatically ligating in each different compartment first and second oligonucleotide tags in the absence of ligation first and second anti-tag oligonucleotides, and optionally

xv) displacing in each compartment unligated anti-tags from bifunctional complexes comprising a molecule and a single stranded oligonucleotide identifier comprising tags identifying the reactants which participated in the synthesis of the molecule.

117. The method of claim 116 comprising the further step of mixing bifunctional complexes from each different reaction compartment.

118. The method of claim 117, wherein, in any round subsequent to the first round, the end product of the preceding round of reaction is used as the nascent bifunctional complex for obtaining a library of different bifunctional complexes.

119. The method of claim 116, wherein steps viii) to xiv) are repeated once or more than once using different reactants and tags identifying said different reactants.

120. The method of claim 116, wherein the one or more reactants applied to each reaction compartment are different.

121. The method of claim 116, wherein the reaction conditions in each reaction compartment are the same.

122. The method of claim 116, wherein the reaction conditions in each reaction compartment are different.

123. The method of claim 116, wherein the bifunctional complex is reacted with more than a single reactant in at least some reaction compartments.

124. A method for identifying a molecule, said method comprising the steps of subjecting the library produced by the method of any of claims 116 to 123 to assaying conditions resulting in the partitioning of some, but not all molecules, from the remainder of the library, and identifying the molecule(s) by decoding the identifier oligonucleotide of the bifunctional complex.

125. The method of claim 124, wherein the library is contacted with a target and wherein bifunctional complexes having an affinity for the target are partitioned form the remainder of the library.

126. The method of any of claims 124 and 125, wherein a single round of selection against a specific target is followed by amplification of the identifier oligonucleotides of the selected bifunctional complexes.

127. The method of any of claims 124 and 125, wherein several rounds of selection against a specific target is followed by amplification of the identifier oligonucleotides of the selected bifunctional complexes.

128. The method of any of claims 126 and 127, wherein the identifier oligonucleotide is amplified using PCR.

129. The method of claim 128, wherein the PCR product is hybridised to a microarray of complementary oligonucleotides, wherein said hybridisation reveals the identity of the display molecule.

130. The method of any of claims 125 to 129, wherein the identifier oligonucleotide of the one or more partitioned bifunctional complexes, optionally attached to a molecule, and further optionally provided with one or more chemical reaction sites, is subjected to a method for synthesizing a plurality of molecules, said method comprising the steps of:

(a) forming a first group of subsets of identifier oligonucleotides comprising a plurality of nucleic acid tags, where the identifier oligonucleotides in each subset each has a selected one of a plurality of different first hybridization sequences, a mixture of different second hybridization sequences, and one or more chemical reaction site(s),

(b) reacting the chemical reaction sites in each of the subsets formed in (a) with a selected reagent, thereby forming a reagent-specific molecule intermediate on the associated sequence in each subset,

(c) forming a second group of subsets of the reacted identifier oligonucleotides comprising a plurality of nucleic acid tags, where the identifier oligonucleotides in each subset each have a selected one of a plurality of different second hybridization sequences, and a mixture of different first hybridization sequences; and

(d) reacting the molecule intermediates in the sequences in each of the subsets formed in (c) with a selected reagent.

131. The method of claim 130, wherein each of said forming steps includes hybridizing the identifier oligonucleotides comprising a plurality of nucleic acid tags within a given subset with a plurality of solid phase reagents each having a surface bound oligonucleotide or oligonucleotide analog capable of forming base-specific duplexes with one of the hybridizing sequences in the given subset to bind each nucleic acid tag to one of the reagents.

132. The method of claim 130, for use in forming a plurality of oligomers with different subunit sequences, wherein each of said reacting steps includes adding a selected subunit to each of the subsets of identifier oligonucleotides comprising a plurality of nucleic acid tags under conditions effective to add that subunit to the chemical reaction site or last-added subunit carried thereon.

133. The method of claim 130, for use in forming a plurality of small molecules with different chemical sequences, wherein each of said reacting steps includes adding a selected chemical substituent to each of the subsets of identifier oligonucleotides comprising a plurality of nucleic acid tags under conditions effective to add that substituent to the chemical reaction site or last-added substituent carried thereon.

134. The method of claim 130 for making a plurality of compounds requiring more than 2 synthetic steps wherein the identifier oligonucleotides comprising a plurality of nucleic acid tags include an additional step-specific subset of hybridization sequences for each synthetic step greater than 2 and which further comprises, for each additional synthetic step;

(e) forming groups of subsets of reacted identifier oligonucleotides comprising a plurality of

nucleic acid tags, wherein the sequences in each subset each have a selected one of a plurality of hybridization sequences in a step-specific subset of identifier oligonucleotides comprising a plurality of nucleic acid tags, and a mixture of different other hybridization sequences;

(f) reacting the compound intermediates in the sequences in each of the subsets formed in (e) with a selected reagent; and

(g) repeating steps (e) and (f) if necessary, until synthesis of the compounds is complete.

135. The method of any of claims 130 or 134, wherein each subset of identifier oligonucleotides comprising a plurality of nucleic acid tags includes at least 3, such as at least 4, for example at least 5 separate hybridization sequences.

136. The method of claim 130, wherein said identifier oligonucleotides comprising a plurality of nucleic acid tags within each subset further comprises for each subset of hybridization sequences, an adjacent spacer sequence separating that hybridization sequence from an adjacent one, each of said spacer sequences being the same for all subsets of identifier oligonucleotides comprising a plurality of nucleic acid tags and each hybridization sequence being different for each group of subsets of identifier oligonucleotides comprising a plurality of nucleic acid tags.

137. The method according to claim 130, for use in enriching the plurality of molecules in those having a desired molecule activity, further comprising identifying from said plurality of molecules, one or more molecules having a desired activity to yield a subpopulation of identifier oligonucleotides comprising a plurality of nucleic acid tags, and using the subpopulation to carry out the method of claim 130.

138. The method according to claim 137, wherein said use includes the steps of

amplifying said subpopulation of identifier oligonucleotides comprising a plurality of nucleic acid tags by non-specific polymerase chain reaction (PCR),

adding a chemical reaction site, and

using said amplified subpopulation having chemical reaction sites to carry out the method of claim 130.

139. The method according to claim 138, for use in producing new permutations of active molecules, wherein said identifier oligonucleotides comprising a plurality of nucleic acid tags have one of a plurality of spacer sequences, each of said spacer sequences having a unique restriction enzyme site;

(e) identifying from said plurality of molecules, one or more molecules having a desired activity to yield a subpopulation of identifier oligonucleotides comprising a plurality of nucleic acid tags;

(f) treating said subpopulation of identifier oligonucleotides comprising a plurality of nucleic acid tags with one or more restriction enzymes under conditions effective to produce a partial digest;

(g) rejoining said partially digested identifier oligonucleotides comprising a plurality of nucleic acid tags;

(h) adding a new chemical reaction site to said partially digested identifier oligonucleotides comprising a plurality of nucleic acid tags and using the subpopulation of identifier oligonucleotides to carry out the method of claim 130.

140. A bifunctional complex comprising a molecule and a single stranded identifier oligonucleotide identifying the molecule, wherein the single stranded identifier comprises a plurality of covalently linked tags which are at least partly hybridised to one or more corresponding anti-tag(s), wherein the anti-tags are not covalently linked to each other.

141. The bifunctional complex according to claim 140, wherein the molecule is a branched or cyclical molecule.

142. The bifunctional complex according to claim 141, wherein the molecule is cyclical and comprises a ring system selected from a single ring system and a fused ring system.

143. The bifunctional complex according to claim 142, wherein one or more heteroatoms are present in either the single ring system or in the fused ring system.

144. The bifunctional complex according to claim 142, wherein the single ring system is not directly bonded at more than one ring atom to another closed ring, and wherein the fused ring system is directly bonded at more than one ring atom to another closed ring.

145. The bifunctional complex according to any of claims 142 to 144, wherein the single ring system is selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl, and heteroaryl each having from about three to about eight, or from about four to about six ring atoms.

146. The bifunctional complex according to any of claims 142 to 144, where the fused ring system is selected from aryl and a cyclyl ring system, wherein about six or less, about five or less, about four or less, about three or less, or about two rings are fused.

147. The bifunctional complex according to claim 146, wherein each ring system is independently selected from the group consisting of aryl, heteroaryl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl, wherein each of said ring systems can independently be substituted or unsubstituted, such as having from about four to about ten, for example from about four to about thirteen, or from about four to about fourteen ring atoms.

148. The bifunctional complex according to claim 143, wherein the one or more heteroatoms are selected from the group consisting of N, O, S, and P, including any oxidized form of nitrogen, sulfur, and phosphorus and the quaternized form of any basic nitrogen.

149. The bifunctional complex according to claim 143, wherein the one or more heteroatoms are selected from the group consisting of N, O, or S, including any oxidized form of nitrogen, sulfur, and phosphorus and the quaternized form of any basic nitrogen.

150. The bifunctional complex according to any of claims 145 and 146, wherein aryl is an aromatic ring structure having about six ring carbon atoms.

151. The bifunctional complex according to claim 150, wherein the aryl is a fused aryl, said fused aryl comprising from about two to about three aromatic rings each having from about six to about ten, such as from about six to about thirteen, for example from about six to about fourteen ring carbon atoms.

152. The bifunctional complex according to claim 151, wherein the aryl is a fused heteroaryl, said fused heteroaryl comprising from about two to about three aromatic rings each having from about six to about ten, such as from about six to about thirteen, for example from about six to about fourteen ring carbon atoms.

153. The bifunctional complex according to claim 146, wherein the cyclyl ring system comprises a fused cycloalkyl comprising from about two to about three cycloalkyl rings each having from about four to about ten, such as from about four to about thirteen, for example from about four to about fourteen ring carbon atoms

154. The bifunctional complex according to claim 153, wherein the cycloalkyl is a lower cycloalkyl having cycloalkyl groups having from about three to about six ring members.

155. The bifunctional complex according to claim 146, wherein the cyclyl ring system comprises a fused heterocycloalkyl comprising from about two to about three heterocycloalkyl rings, wherein at least one of said rings is a heterocycloalkyl having from about four to about ten, such as from about four to about thirteen, for example from about four to about fourteen ring atoms, wherein the heterocycloalkyl is a cycloalkyl comprising one or more heteroatoms in place of a ring carbon atom, said heteroatoms being selected from the group consisting of N, O, S, and P, including any oxidized form of nitrogen, sulfur, and phosphorus and the quaternized form of any basic nitrogen.

156. The bifunctional complex according to claim 155, wherein the heterocycloalkyl is a lower heterocycloalkyl having cycloalkyl groups having from about three to about six ring members.

157. The bifunctional complex according to any of claims 153 to 156, wherein the cycloalkyl is a heterocycloalkenyl comprising one or more heteroatoms in place of a ring carbon atom.

158. The bifunctional complex according to claim 157, wherein the cycloalkyl is a lower heterocycloalkenyl having from about three to about six ring members.

159. The bifunctional complex according to claim 157, wherein the heteroaryl is a fused ring system, wherein each ring system has about three, about five, about six, about seven, or about eight ring atoms, and further optionally comprises one or more heteroatoms, wherein one or more heteroatoms are present in at least one of said ring systems.

160. The bifunctional complex according to claim 157, wherein the heteroaryl is a lower heteroaryl and has from about three, such as about five, for example about six ring members.

161. A library of different bifunctional complexes according to any of claims 140 to 160.

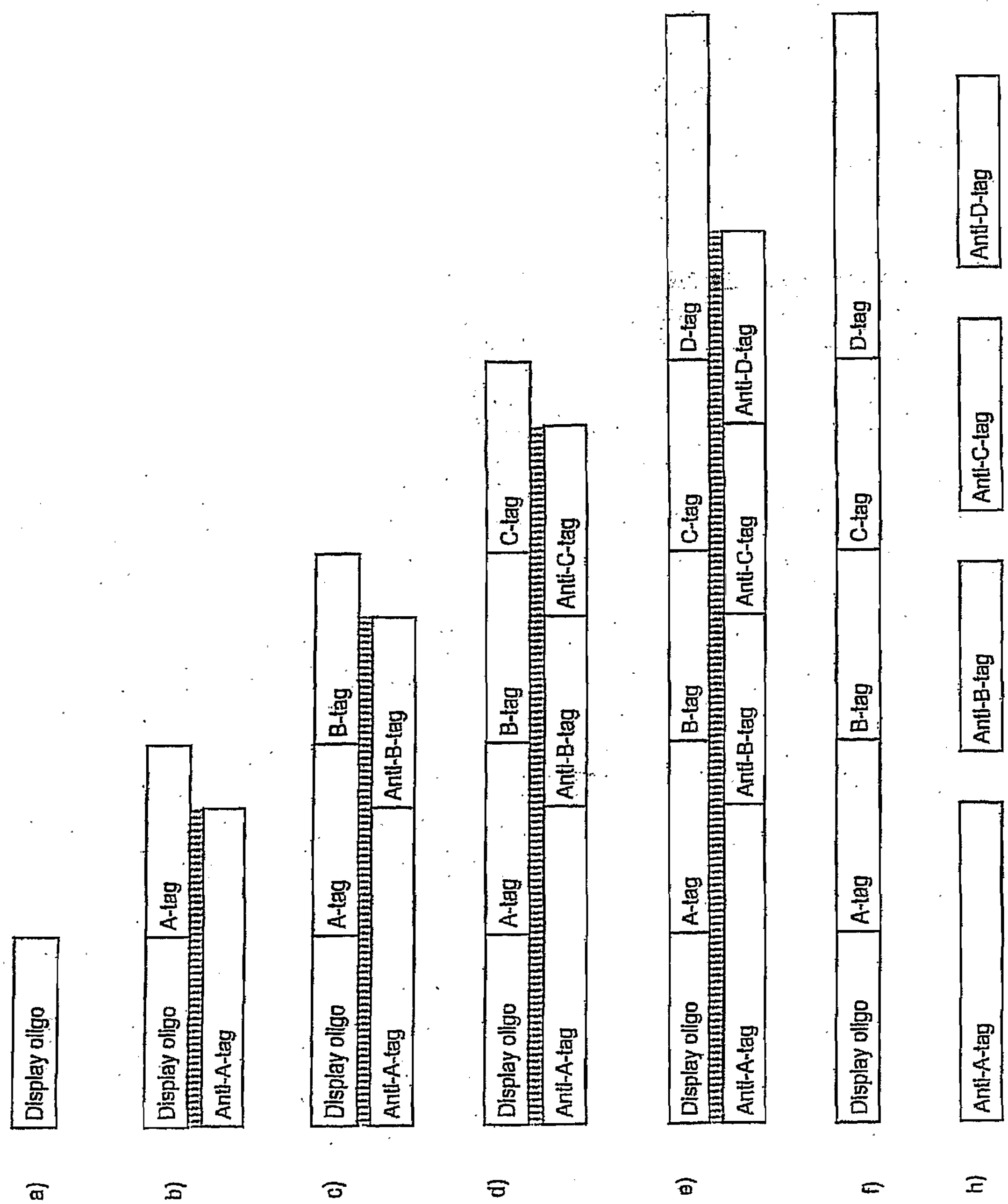

a)
Display oligo
b)
Display oligo
A-tag
Anti-A-tag
c)
Display oligo
A-tag
B-tag
Anti-A-tag
Anti-B-tag
d)
Display oligo
A-tag
B-tag
C-tag
Anti-A-tag
Anti-B-tag
Anti-C-tag
e)
Display oligo
A-tag
B-tag
C-tag
D-tag
Anti-A-tag
Anti-B-tag
Anti-C-tag
Anti-D-tag
f)
Display oligo
A-tag
B-tag
C-tag
D-tag
h)
Anti-A-tag
Anti-B-tag
Anti-C-tag
Anti-D-tag

Fig. 1

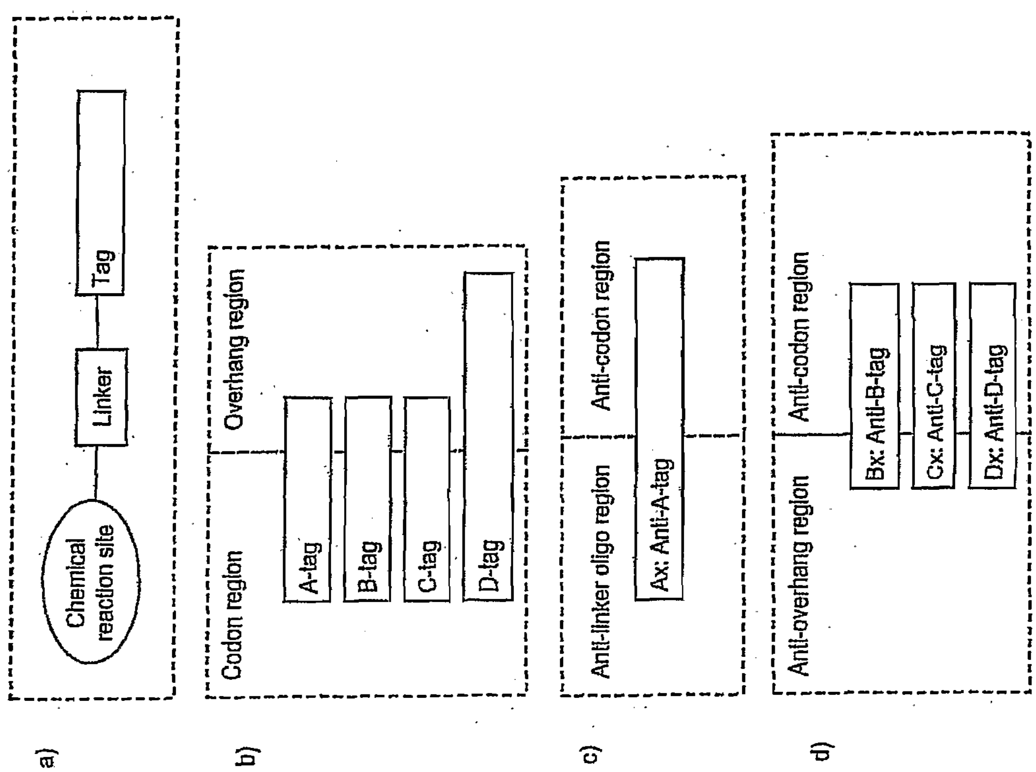

a)
Chemical reaction site
Linker
Tag
b)
Codon region
Overhang region
A-tag
B-tag
C-tag
D-tag
c)
Anti-linker oligo region
Anti-codon region
Ax: Anti-A-tag
d)
Anti-overhang region
Anti-codon region
Bx: Anti-B-tag
Cx: Anti-C-tag
Dx: Anti-D-tag

Fig. 2

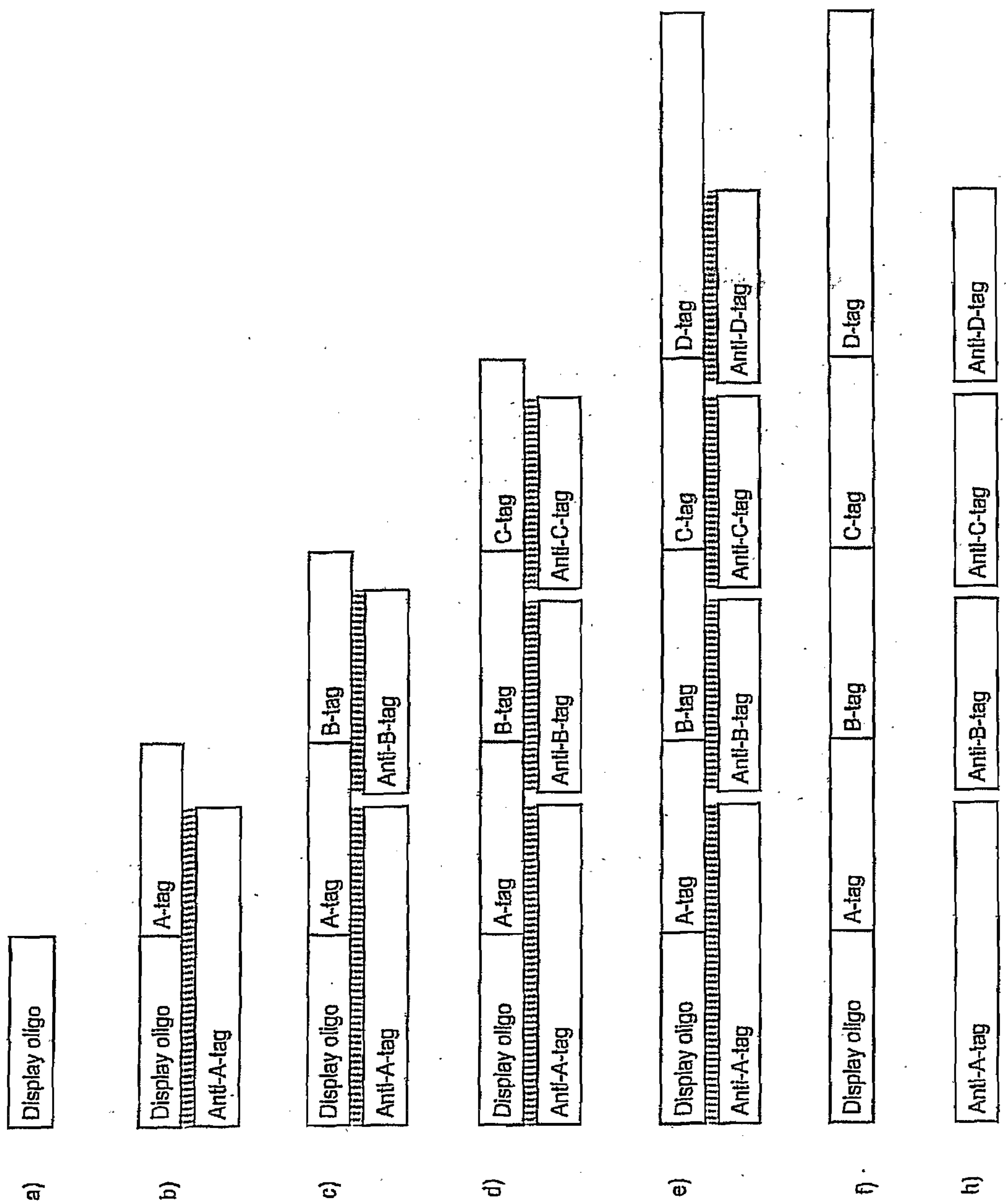

a)
Display oligo
b)
Display oligo
A-tag
Anti-A-tag
c)
Display oligo
A-tag
B-tag
Anti-A-tag
Anti-B-tag
d)
Display oligo
A-tag
B-tag
C-tag
Anti-A-tag
Anti-B-tag
Anti-C-tag
e)
Display oligo
A-tag
B-tag
C-tag
D-tag
Anti-A-tag
Anti-B-tag
Anti-C-tag
Anti-D-tag
f)
Display oligo
A-tag
B-tag
C-tag
D-tag
h)
Anti-A-tag
Anti-B-tag
Anti-C-tag
Anti-D-tag

Fig. 3

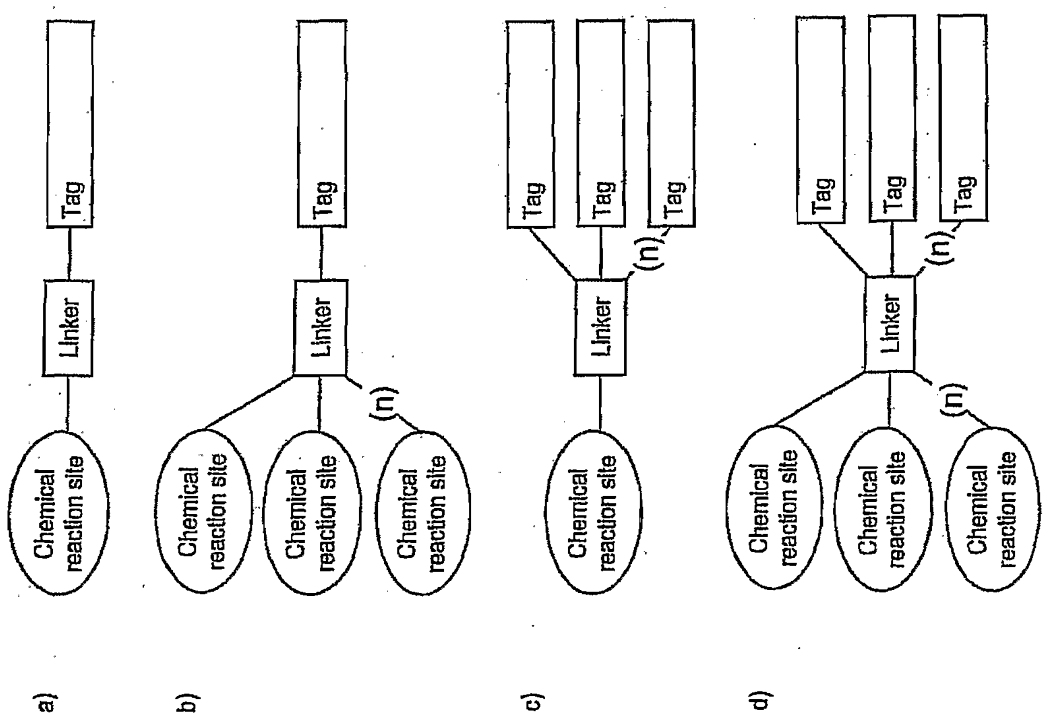

a)
Chemical reaction site
Linker
Tag
b)
Chemical reaction site
Chemical reaction site
Chemical reaction site
(n)
Linker
Tag
c)
Chemical reaction site
Linker
(n)
Tag
Tag
Tag
d)
Chemical reaction site
Chemical reaction site
Chemical reaction site
(n)
Linker
(n)
Tag
Tag
Tag

Fig. 4

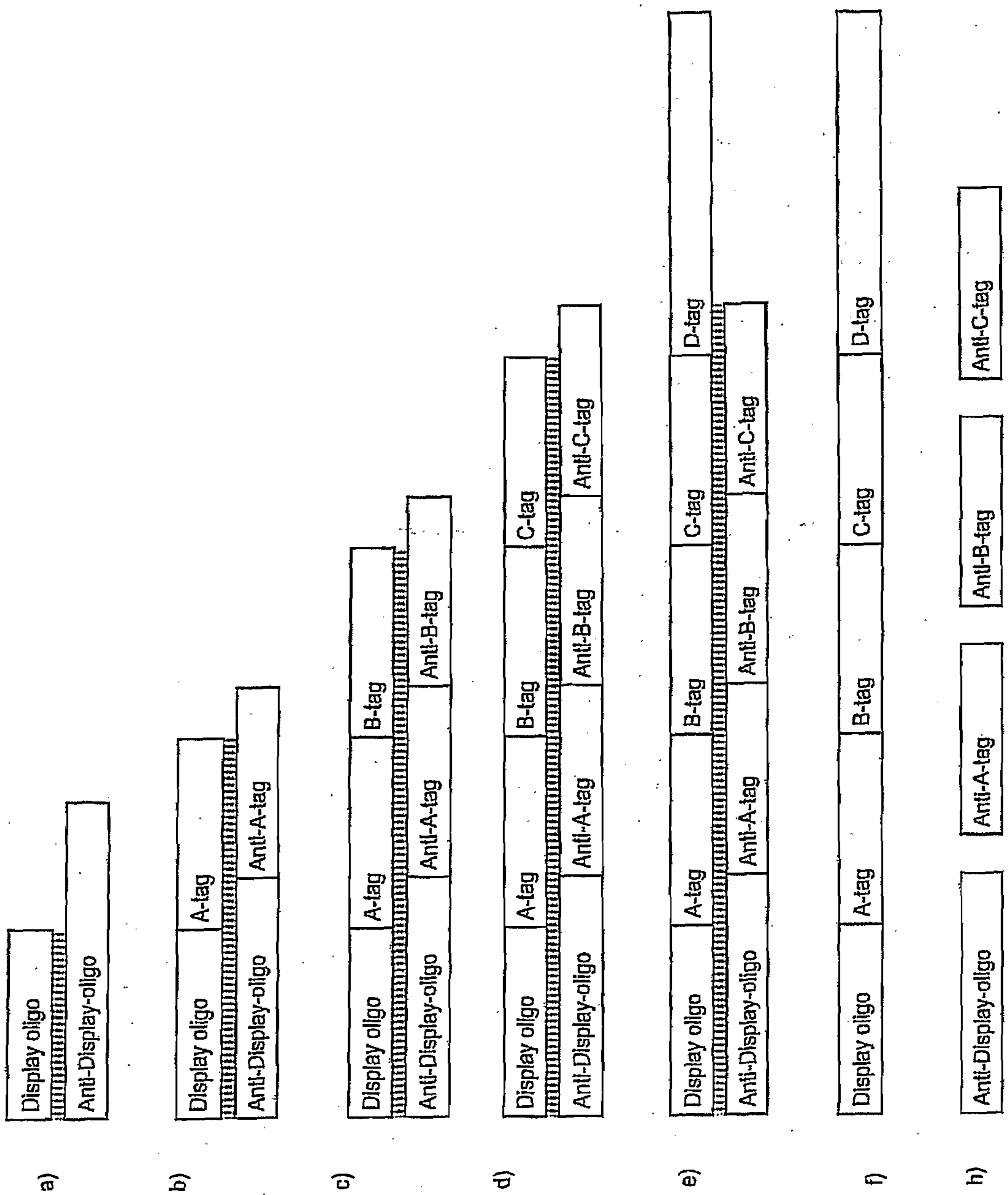

a)
Display oligo
Anti-Display-oligo
b)
Display oligo
A-tag
Anti-Display-oligo
Anti-A-tag
c)
Display oligo
A-tag
B-tag
Anti-Display-oligo
Anti-A-tag
Anti-B-tag
d)
Display oligo
A-tag
B-tag
C-tag
Anti-Display-oligo
Anti-A-tag
Anti-B-tag
Anti-C-tag
e)
Display oligo
A-tag
B-tag
C-tag
D-tag
Anti-Display-oligo
Anti-A-tag
Anti-B-tag
Anti-C-tag
f)
Display oligo
A-tag
B-tag
C-tag
D-tag
h)
Anti-Display-oligo
Anti-A-tag
Anti-B-tag
Anti-C-tag

Fig. 5

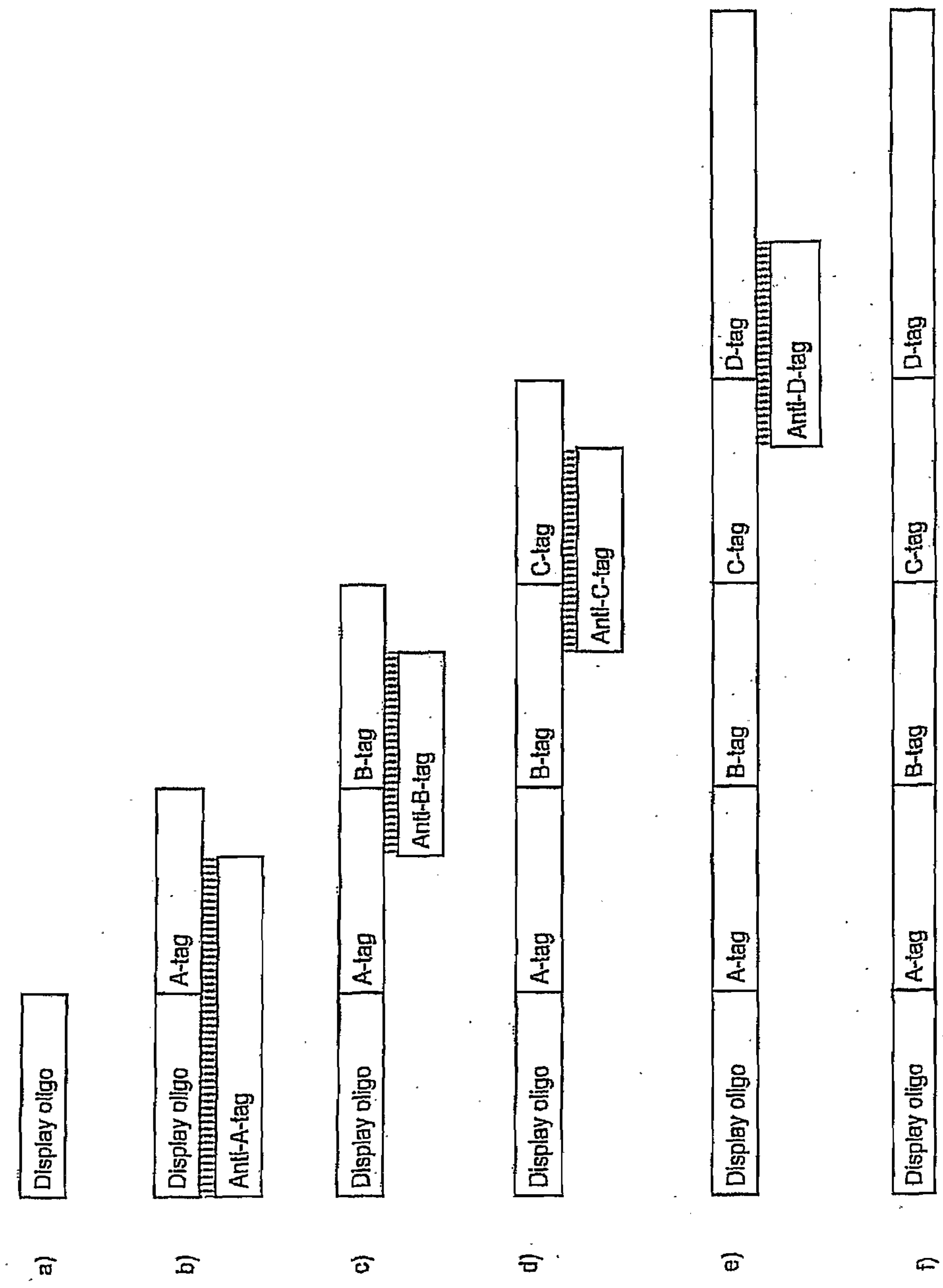

a)
Display oligo
b)
Display oligo
A-tag
Anti-A-tag
c)
Display oligo
A-tag
B-tag
Anti-B-tag
d)
Display oligo
A-tag
B-tag
C-tag
Anti-C-tag
e)
Display oligo
A-tag
B-tag
C-tag
D-tag
Anti-D-tag
f)
Display oligo
A-tag
B-tag
C-tag
D-tag

Fig. 6

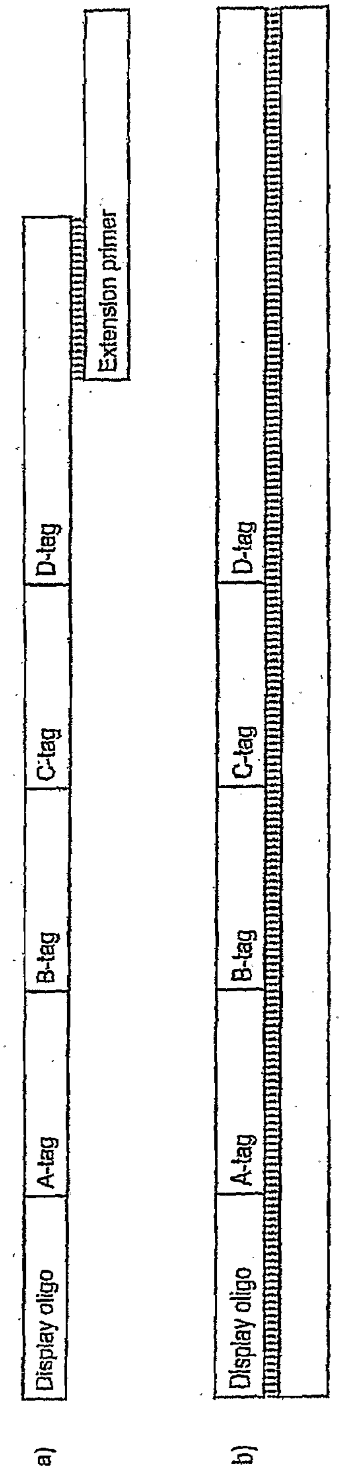

a)
Display oligo
A-tag
B-tag
C-tag
D-tag
Extension primer
b)
Display oligo
A-tag
B-tag
C-tag
D-tag

Fig. 7

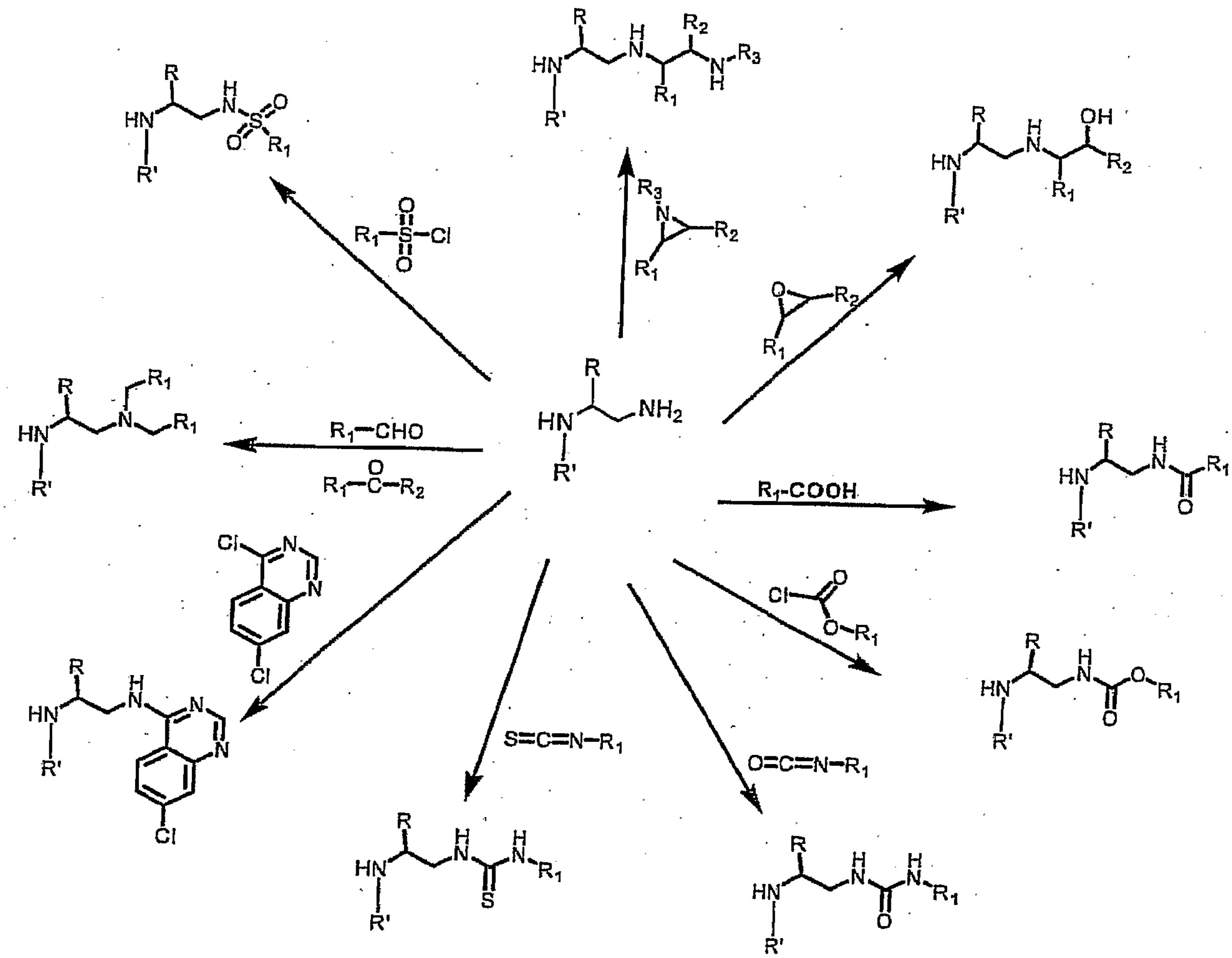

R
HN
NH2
R'
R1-COOH
R1—CHO
R1—C—R2
O
S=C=N—R1
O=C=N—R1
R1-S-Cl
R3
N
R2
R1
Cl
N
OH
O
O-R1

Fig. 8

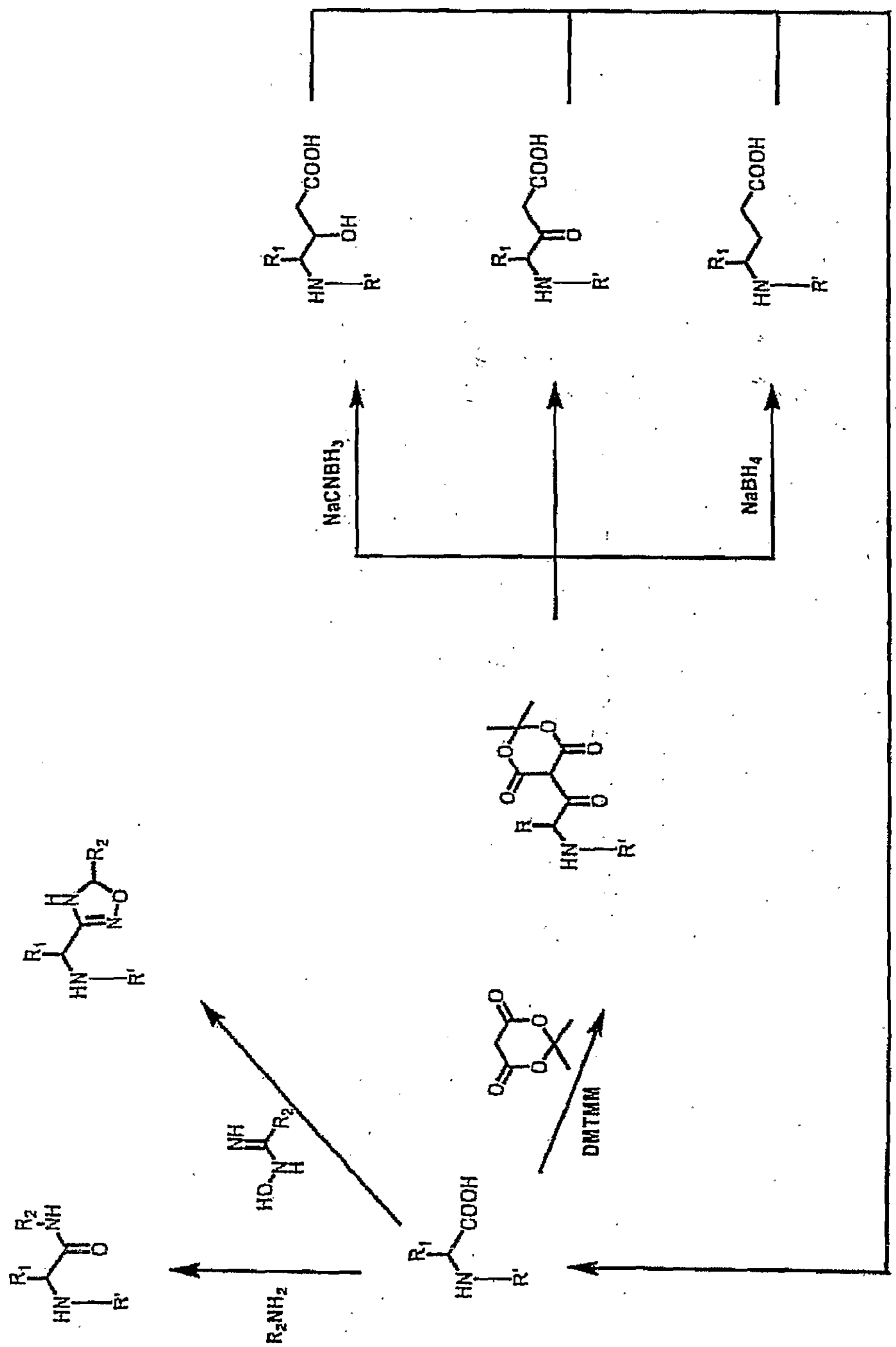


Fig. 9

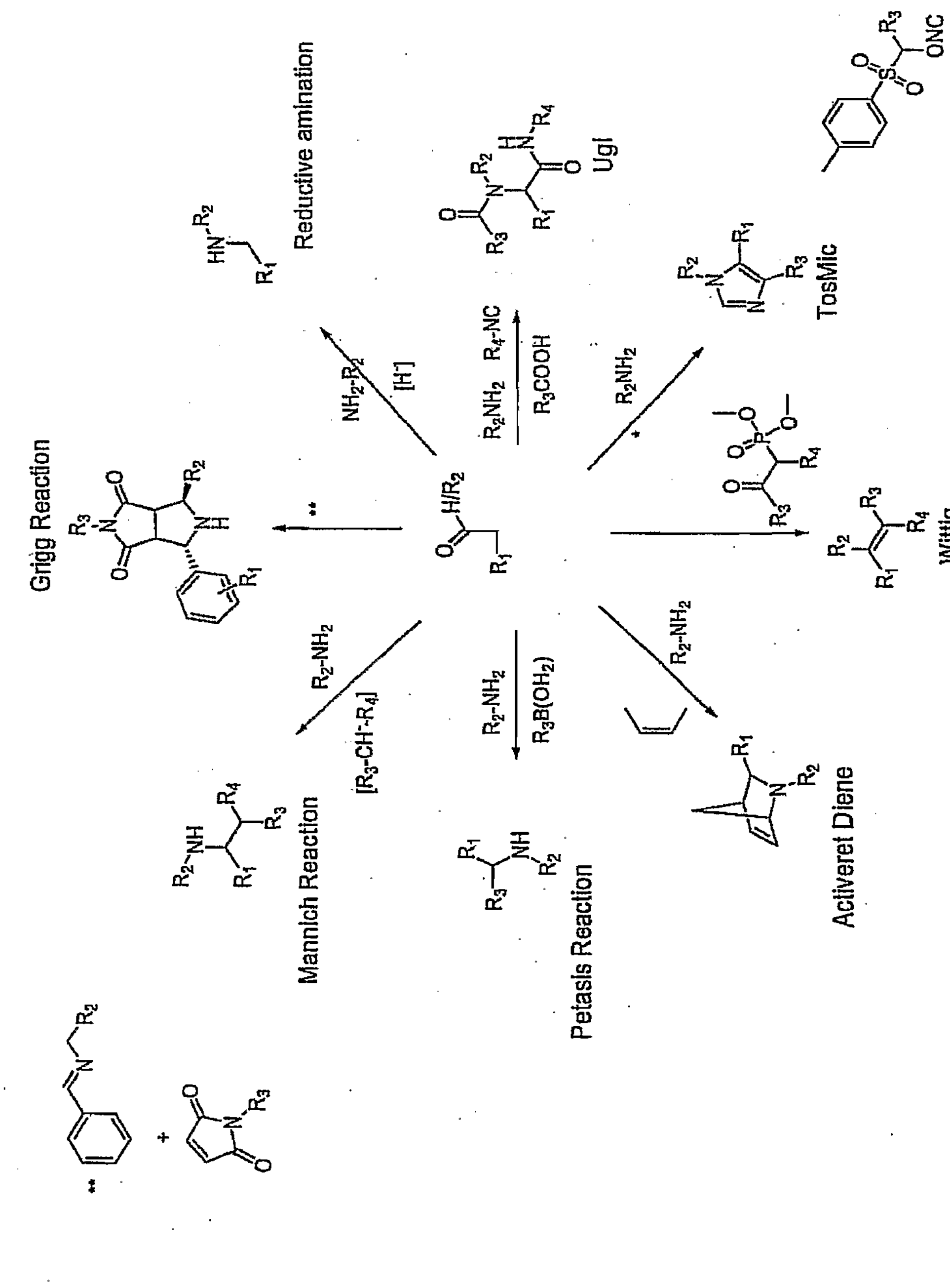

Reductive amination
Ugi
TosMic
Wittig
Activeret Diene
Petasis Reaction
Mannich Reaction
Grigg Reaction
NH_2-R_2
[H⁺]
R_2NH_2
R_4-NC
R_3COOH
R_2-NH_2
$R_3B(OH_2)$
[R_3-CH⁻-R_4]

Fig. 10

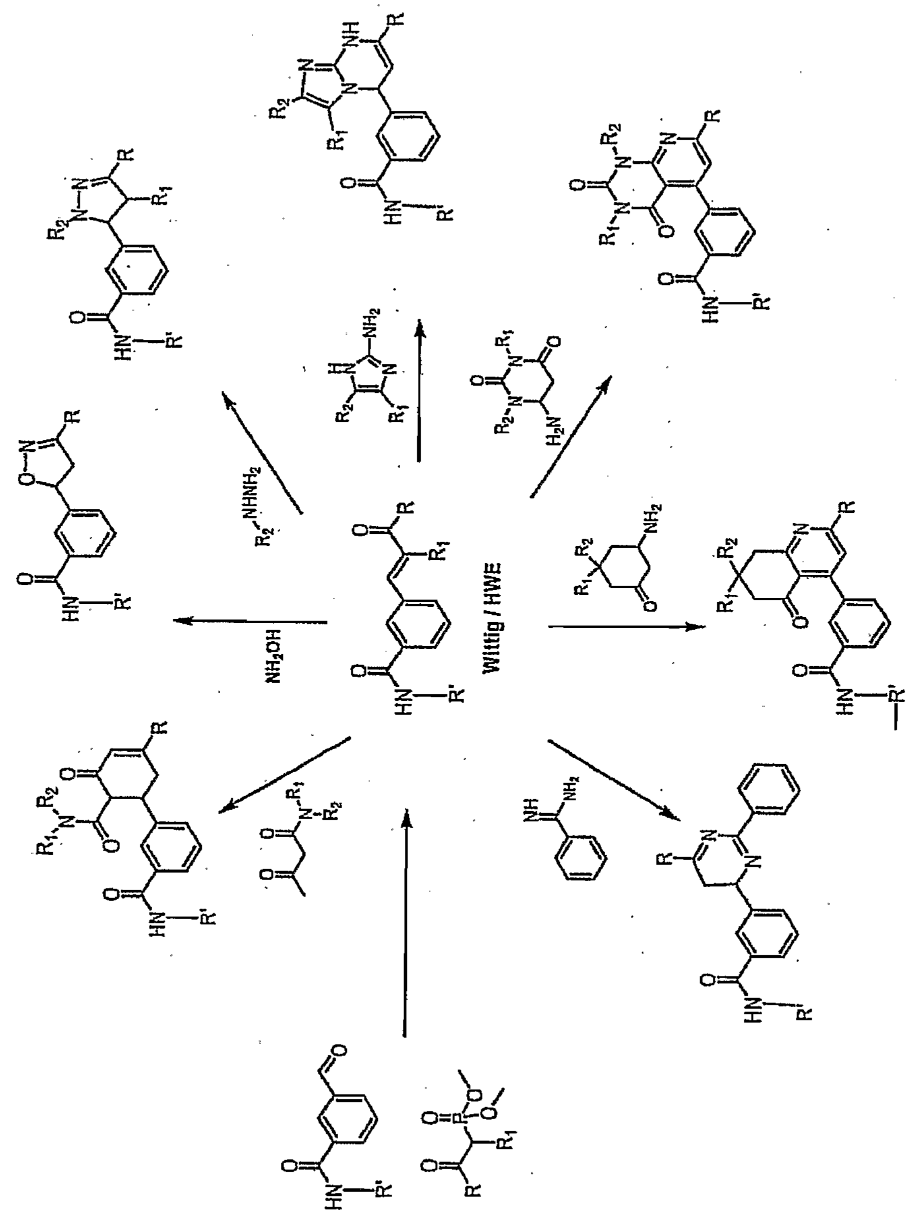


Fig. 11

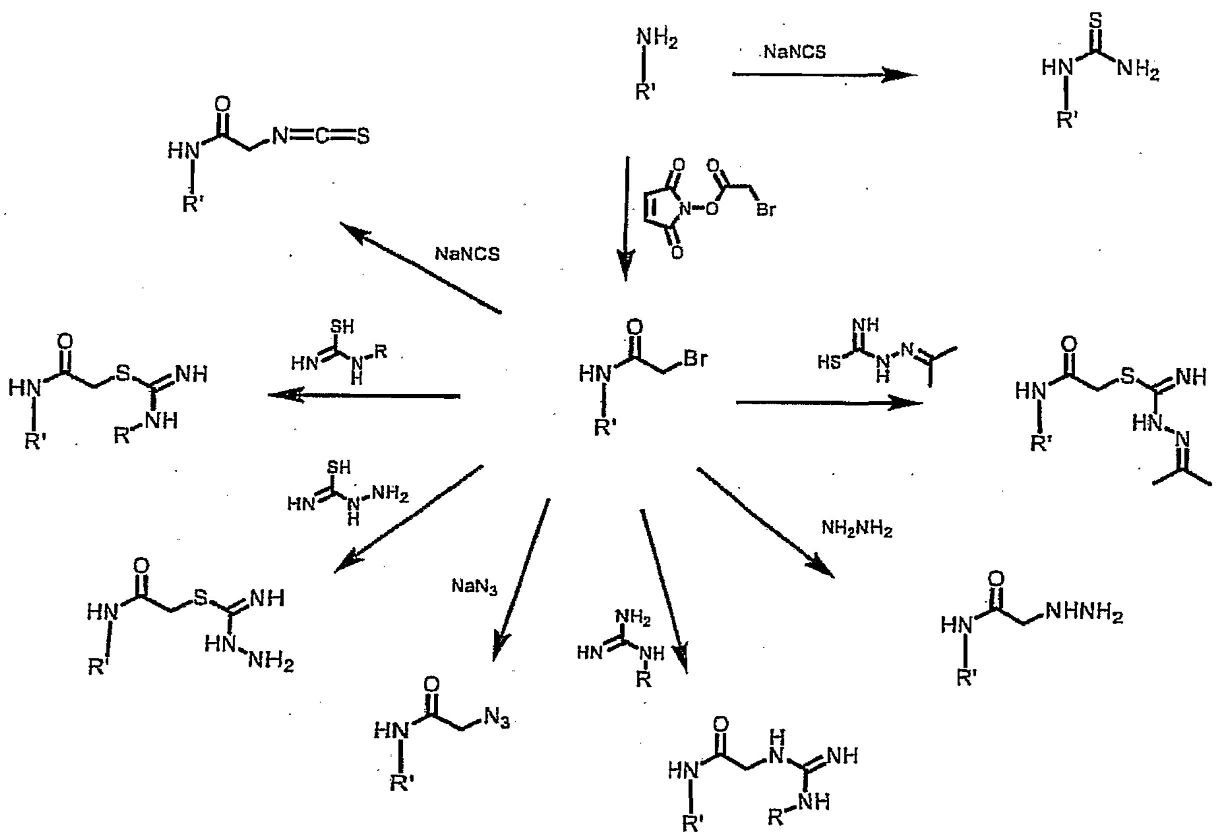
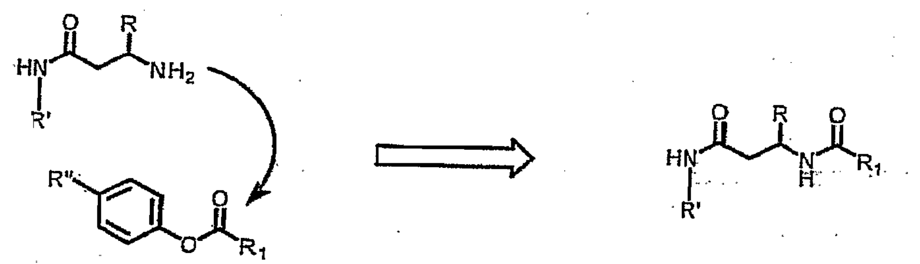


Fig. 12

a)


HN
R'
O
R
NH2
R''
O
O
R1
HN
R'
O
R
N
H
O
R1

b)

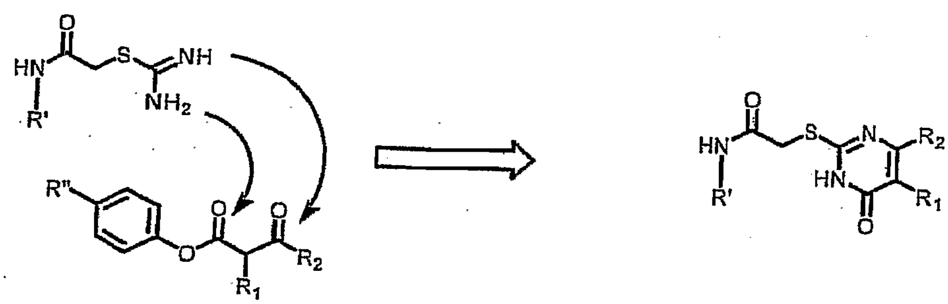

HN
R'
O
S
NH
NH2
R''
O
O
O
R1
R2
HN
R'
O
S
N
HN
O
R2
R1

Fig. 13

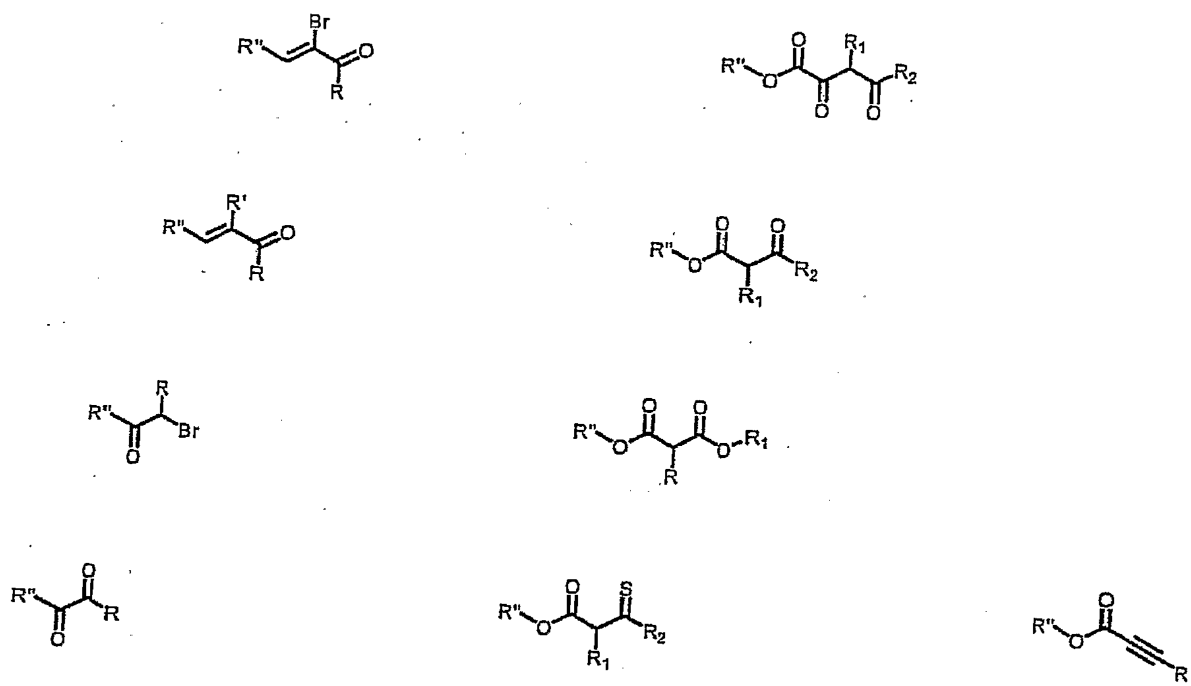


Fig. 14

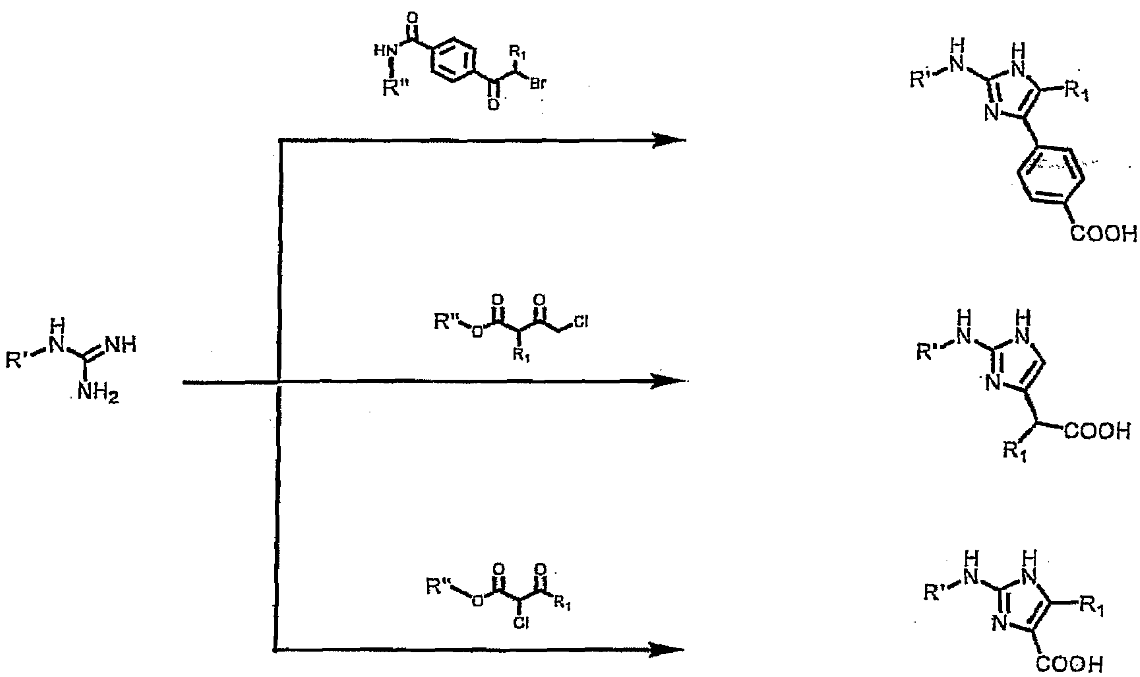


Fig. 15

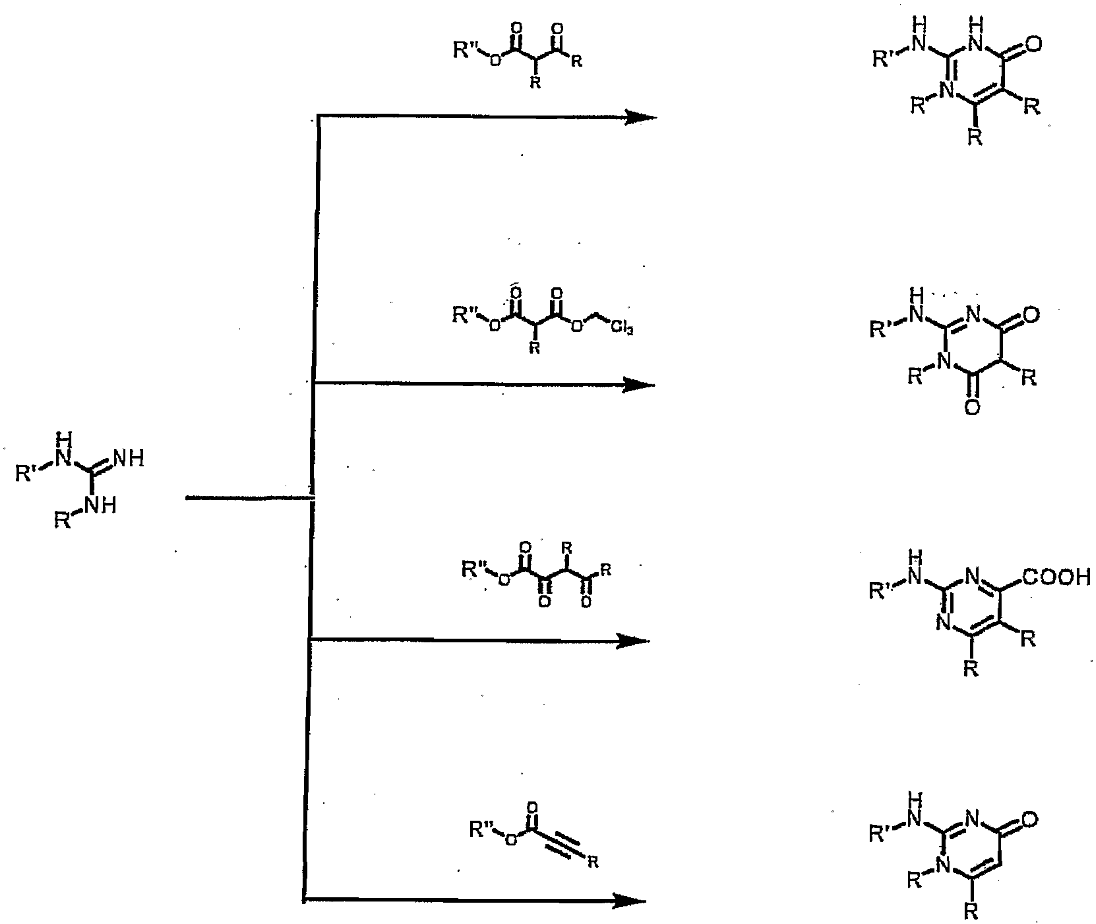


Fig. 16

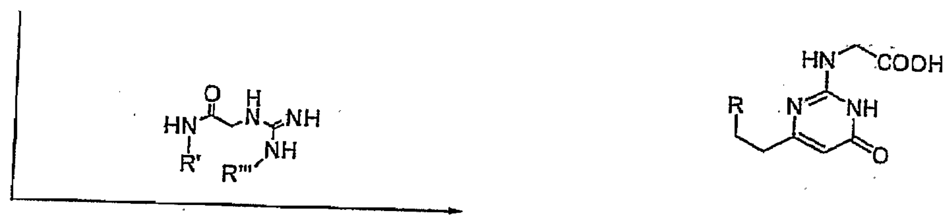


Fig. 17

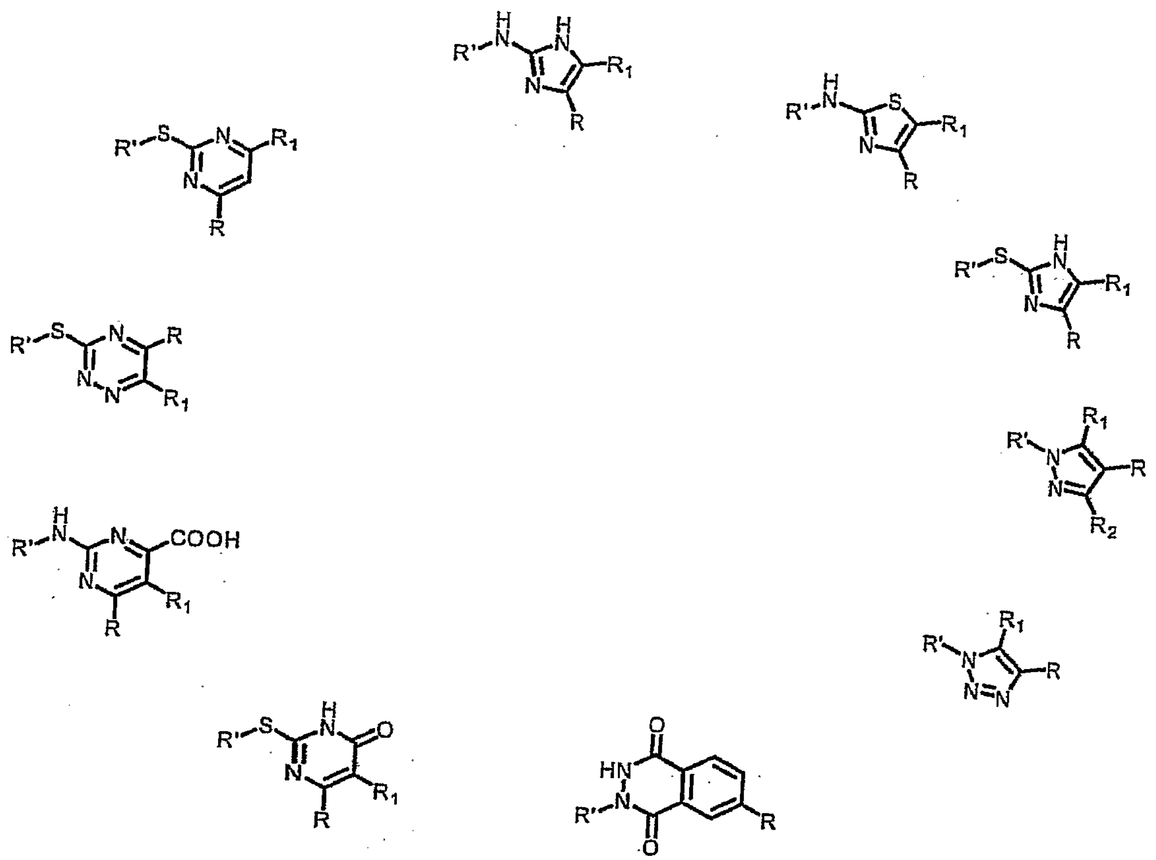


Fig. 18

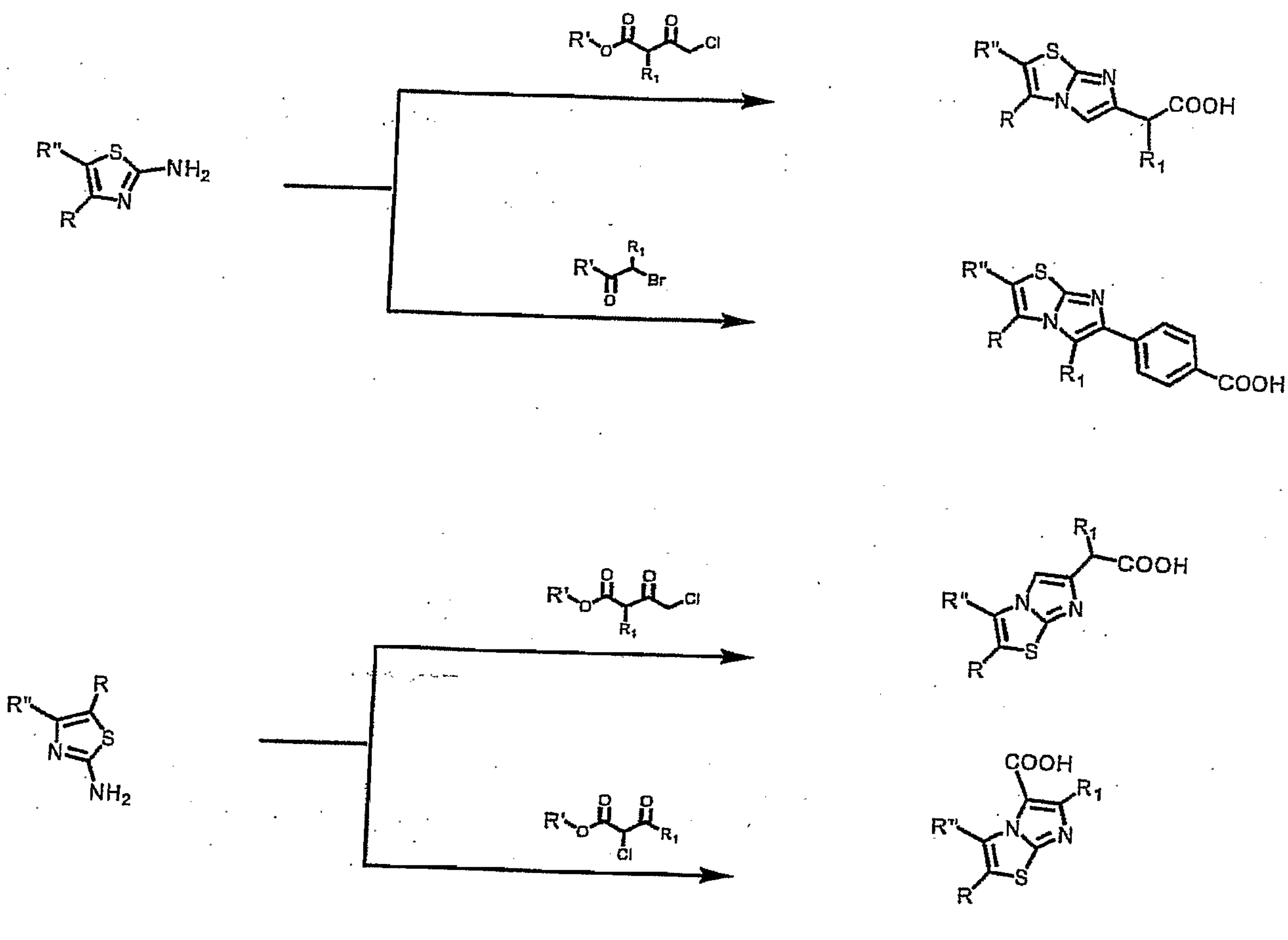


Fig. 19

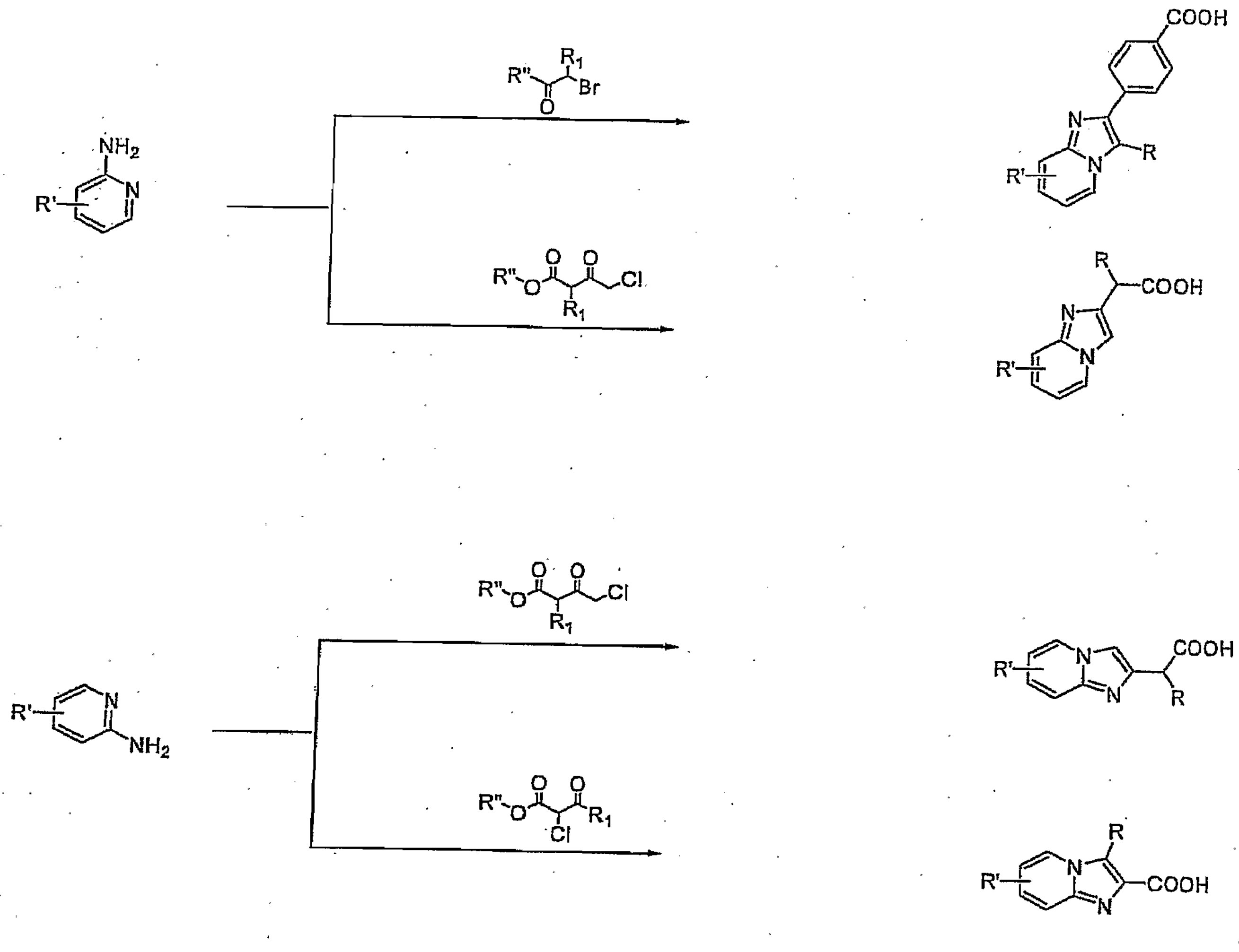

NH2
R'
N
R"
R1
Br
O
COOH
N
N
R
R'
R"
O
O
O
R1
Cl
R
COOH
N
N
R'
R"
O
O
O
R1
Cl
R'
N
NH2
R"
O
O
O
Cl
R1
COOH
R
R'
N
N
R
COOH
N
N
R'

Fig. 20

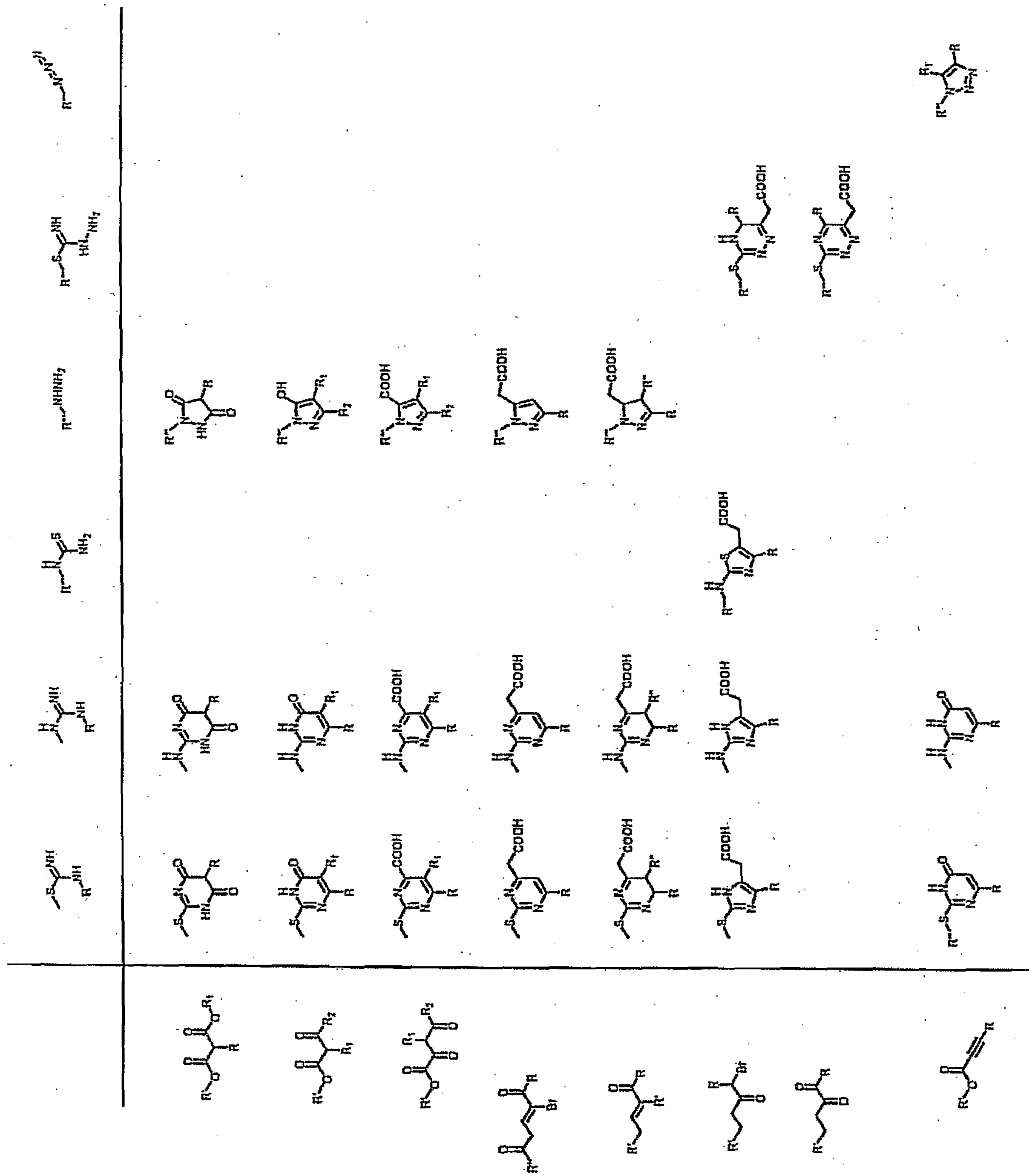
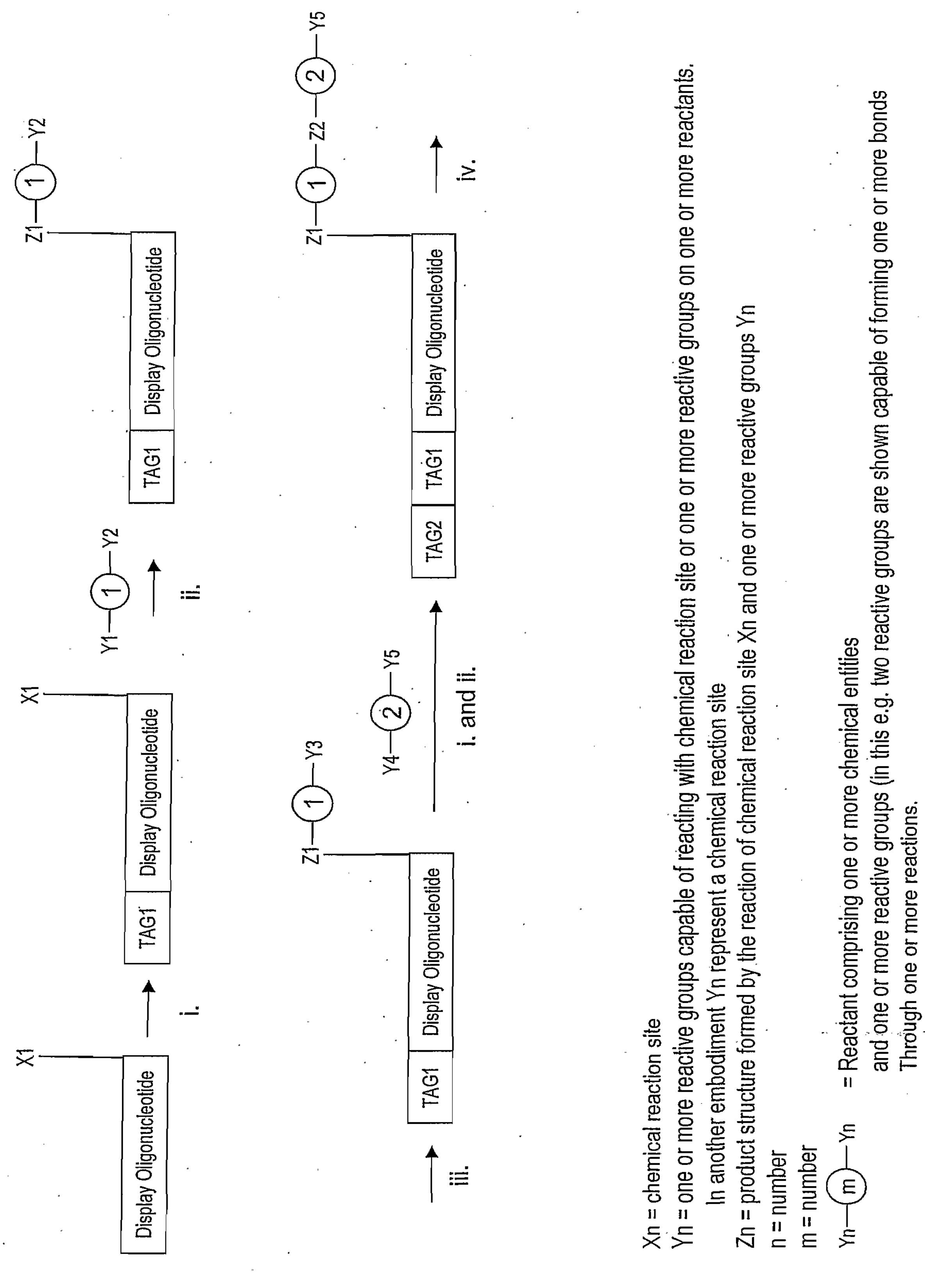
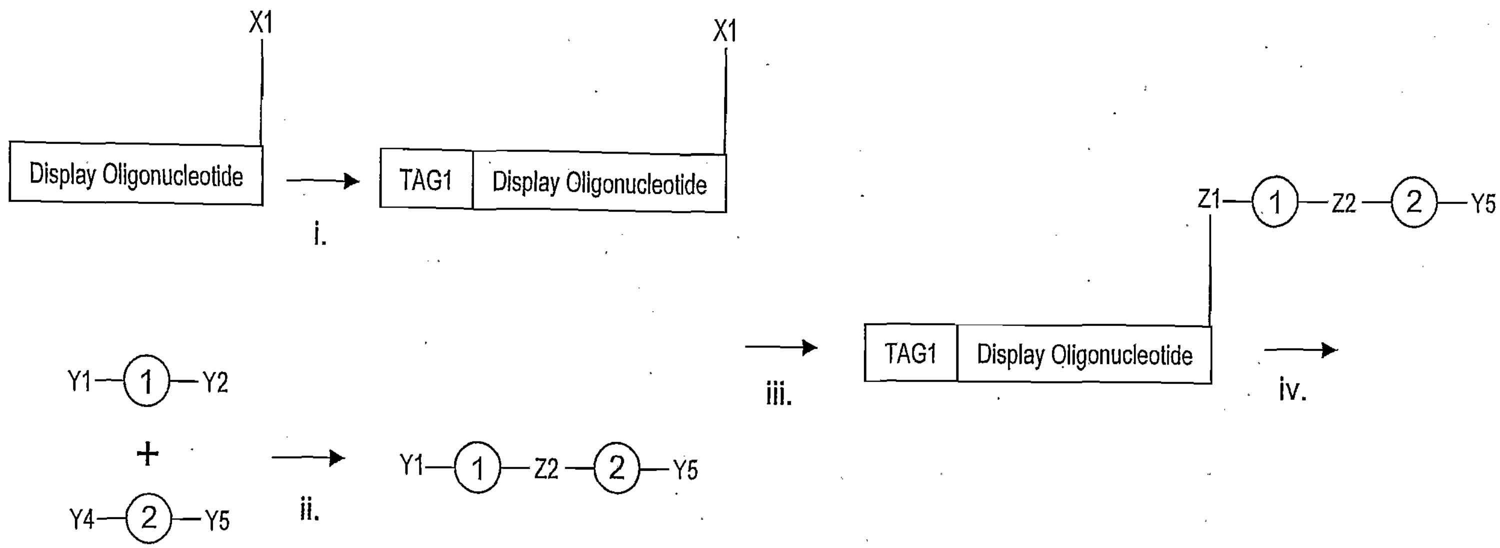


Fig. 21



X1
Display Oligonucleotide
i.
X1
TAG1
Display Oligonucleotide
Y1 1 Y2
ii.
Z1 1 Y2
TAG1
Display Oligonucleotide
iii.
Z1 1 Y3
TAG1
Display Oligonucleotide
Y4 2 Y5
i. and ii.
Z1 1 Z2 2 Y5
TAG2
TAG1
Display Oligonucleotide
iv.
Xn = chemical reaction site
Yn = one or more reactive groups capable of reacting with chemical reaction site or one or more reactive groups on one or more reactants.
In another embodiment Yn represent a chemical reaction site
Zn = product structure formed by the reaction of chemical reaction site Xn and one or more reactive groups Yn
n = number
m = number
Yn m Yn = Reactant comprising one or more chemical entities
and one or more reactive groups (in this e.g. two reactive groups are shown capable of forming one or more bonds
Through one or more reactions.

Fig. 22



Xn = chemical reaction site

Yn = one or more reactive groups capable of reacting with chemical reaction site or one or more reactive groups on one or more reactants
In another embodiment Yn represent a chemical reaction site

Zn = product structure formed by the reaction of chemical reaction site Xn and one or more reactive groups Yn

n = number

m = number

Yn—(m)—Yn = Reactant comprising one or more chemical entities
and one or more reactive groups (in this e.g. two reactive groups are shown capable of forming one or more bonds
Through one or more reactions.

Fig. 23

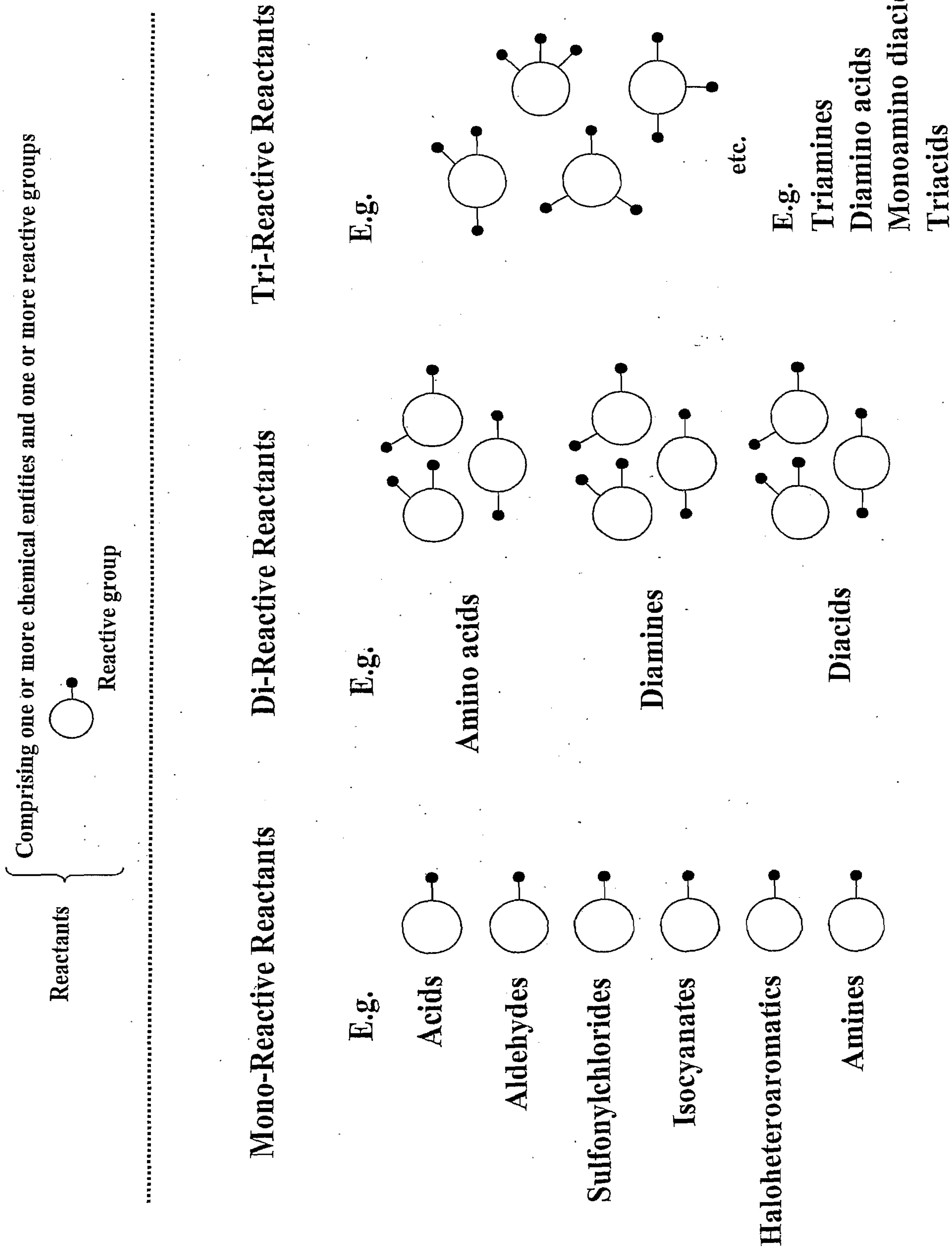
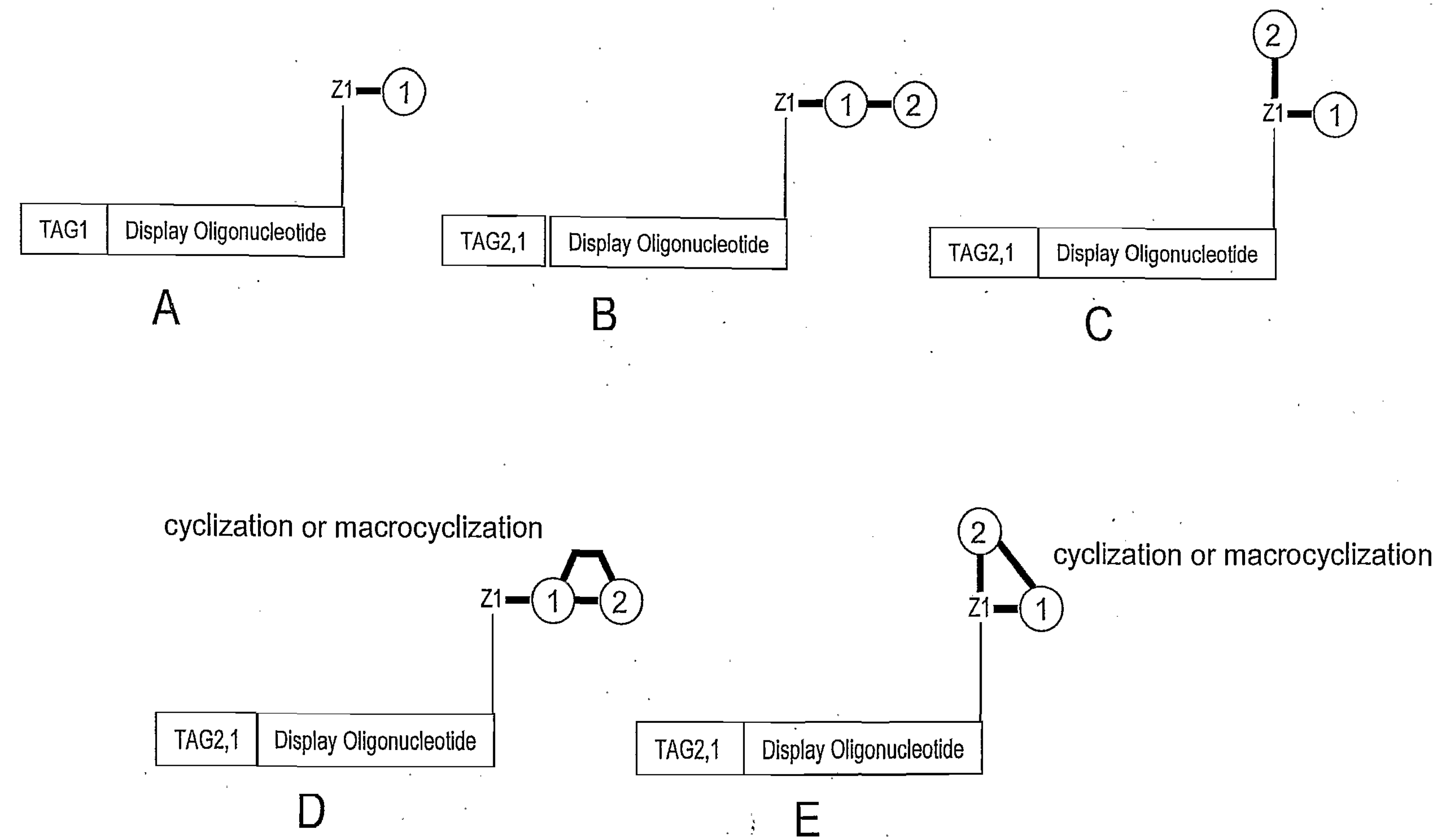

Reactants
Comprising one or more chemical entities and one or more reactive groups
Reactive group
Mono-Reactive Reactants
E.g.
Acids
Aldehydes
Sulfonylchlorides
Isocyanates
Haloheteroaromatics
Amines
Di-Reactive Reactants
E.g.
Amino acids
Diamines
Diacids
Tri-Reactive Reactants
E.g.
etc.
E.g.
Triamines
Diamino acids
Monoamino diacids
Triacids

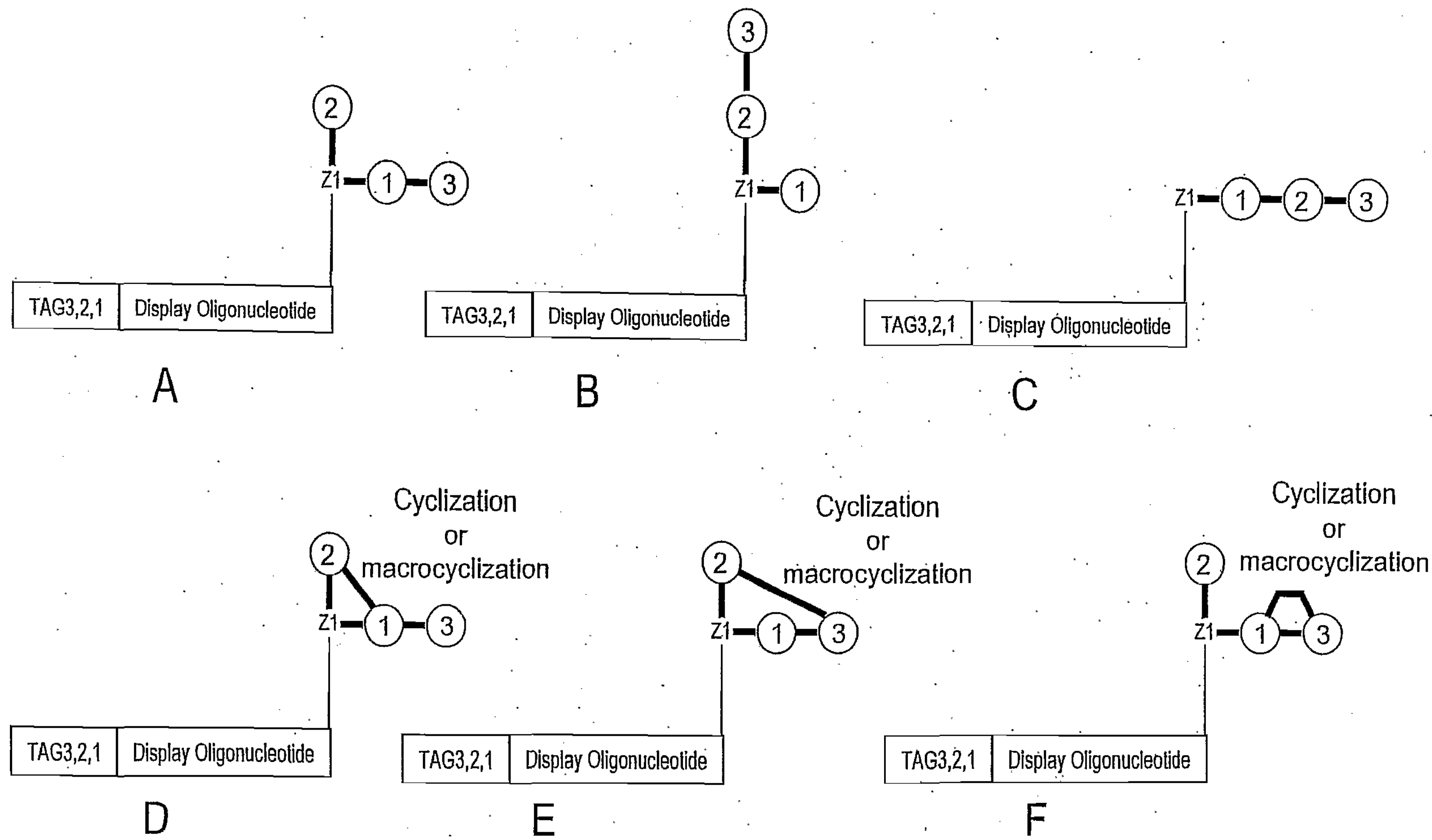
Fig. 24



(n) = Denotes reactant n

= Denotes a product structure formed by the reaction of one or more chemical reaction sites and one or more reactants carrying one or more reactive groups. For example one or more covalent bonds formed between atoms of two or more reactants.
Denotes in another embodiment one or covalent bonds formed between atoms of one or more reactants and one or more chemical reactive sites.
Denotes in further embodiment a cyclic structure formed by the reaction between further reactive groups on two or more reactants.

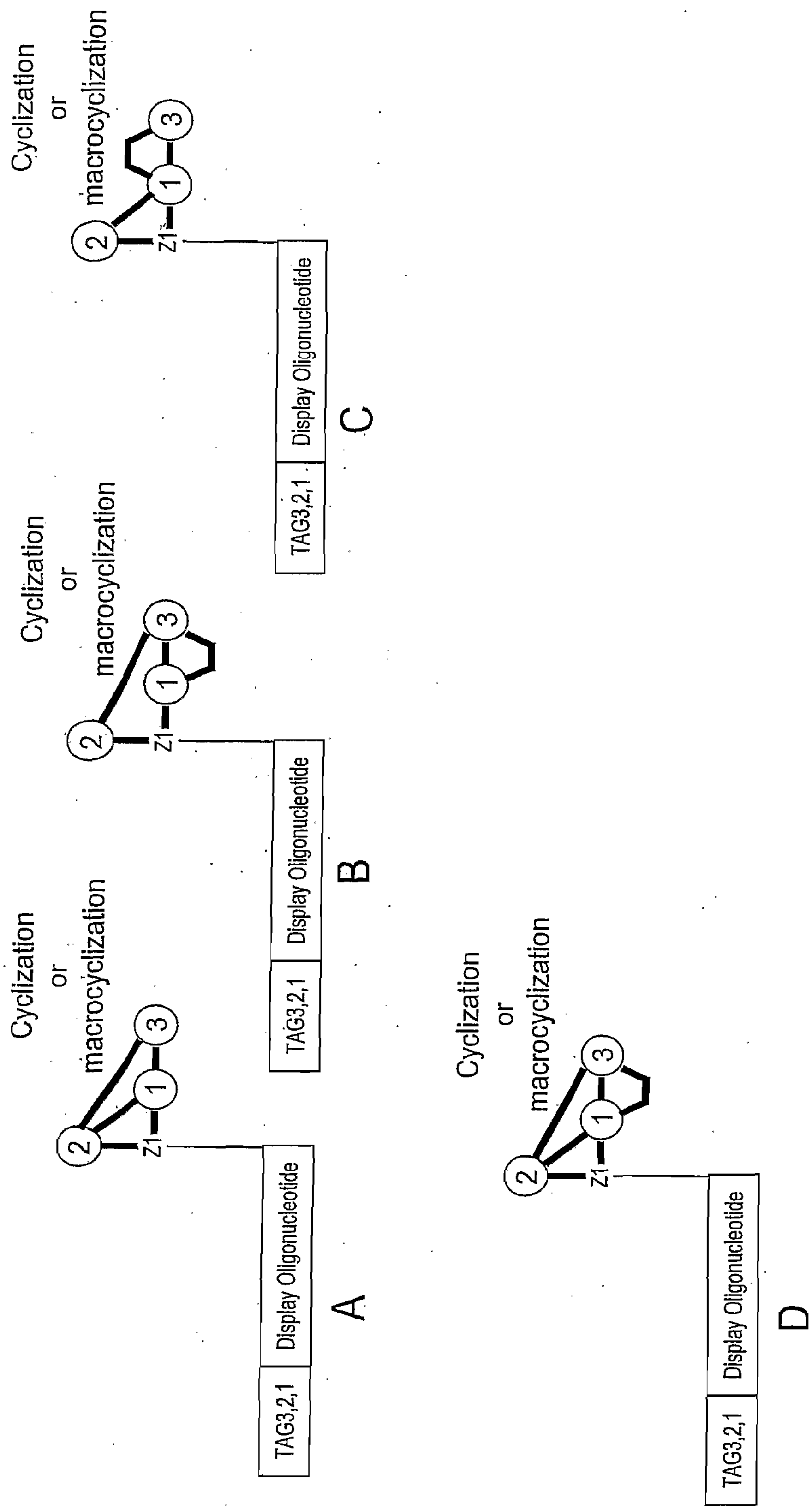
Fig. 25



(n) = Denotes reactant n

— = Denotes a product structure formed by the reaction of one or more chemical reaction sites and one or more reactants carrying one or more reactive groups. For example one or more covalent bonds formed between atoms of two or more reactants.
Denotes in another embodiment one or covalent bonds formed between atoms of one or more reactants and one or more chemical reactive sites.
Denotes in further embodiment a cyclic structure formed by the reaction between further reactive groups on two or more reactants.

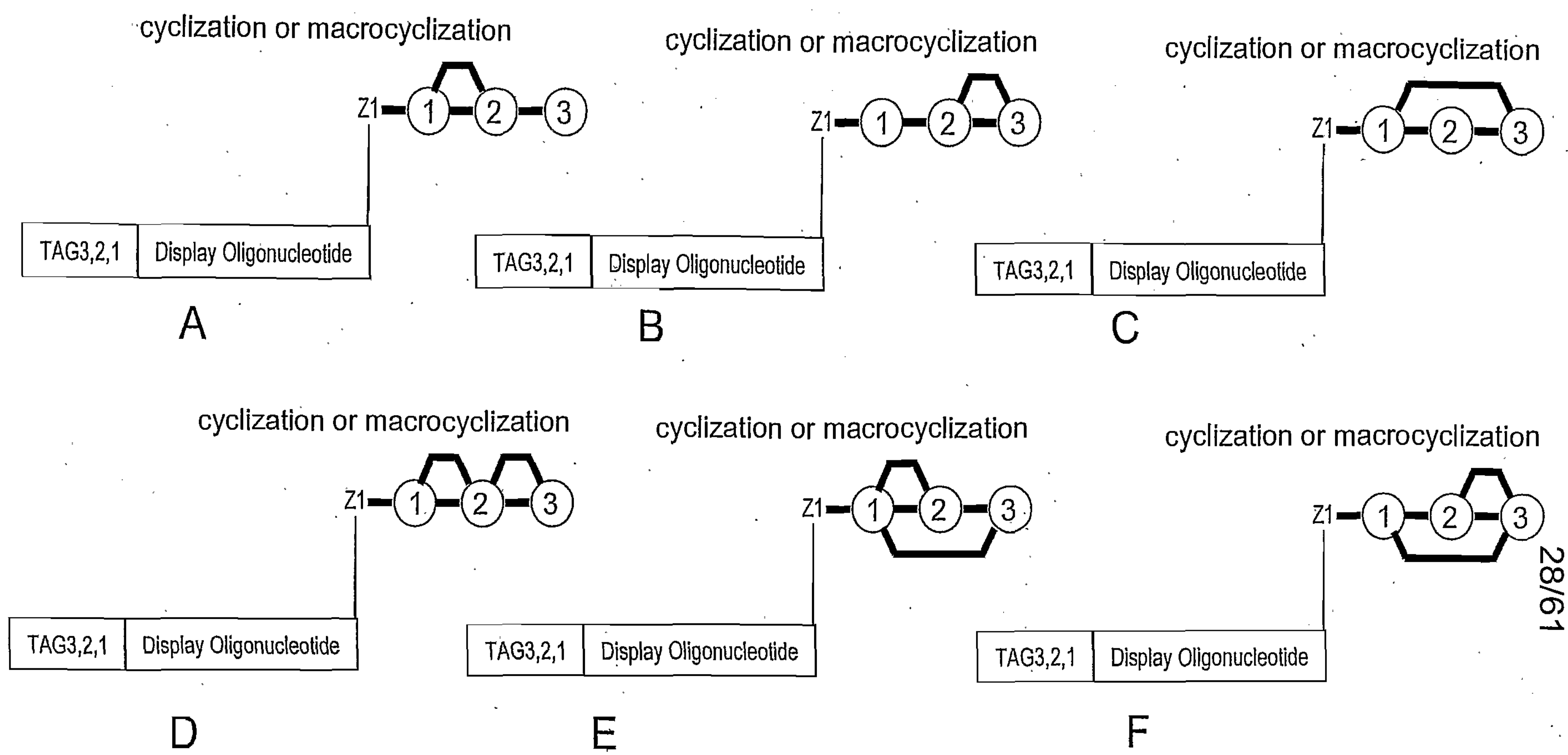
Fig. 26

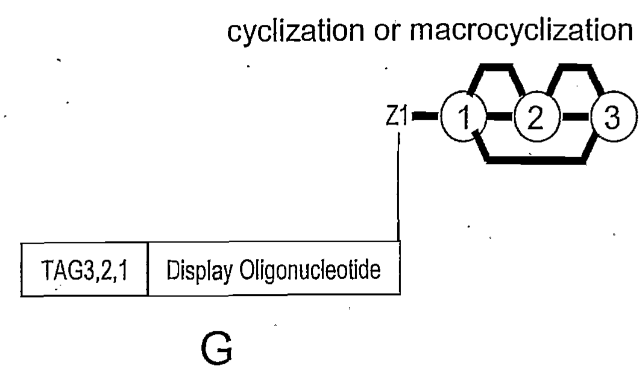


(n) = Denotes reactant n

= Denotes a product structure formed by the reaction of one or more chemical reaction sites and one or more reactants carrying one or more reactive groups. For example one or more covalent bonds formed between atoms of two or more reactants.
Denotes in another embodiment one or covalent bonds formed between atoms of one or more reactants and one or more chemical reactive sites.
Denotes in further embodiment a cyclic structure formed by the reaction between further reactive groups on two or more reactants.

Fig. 27

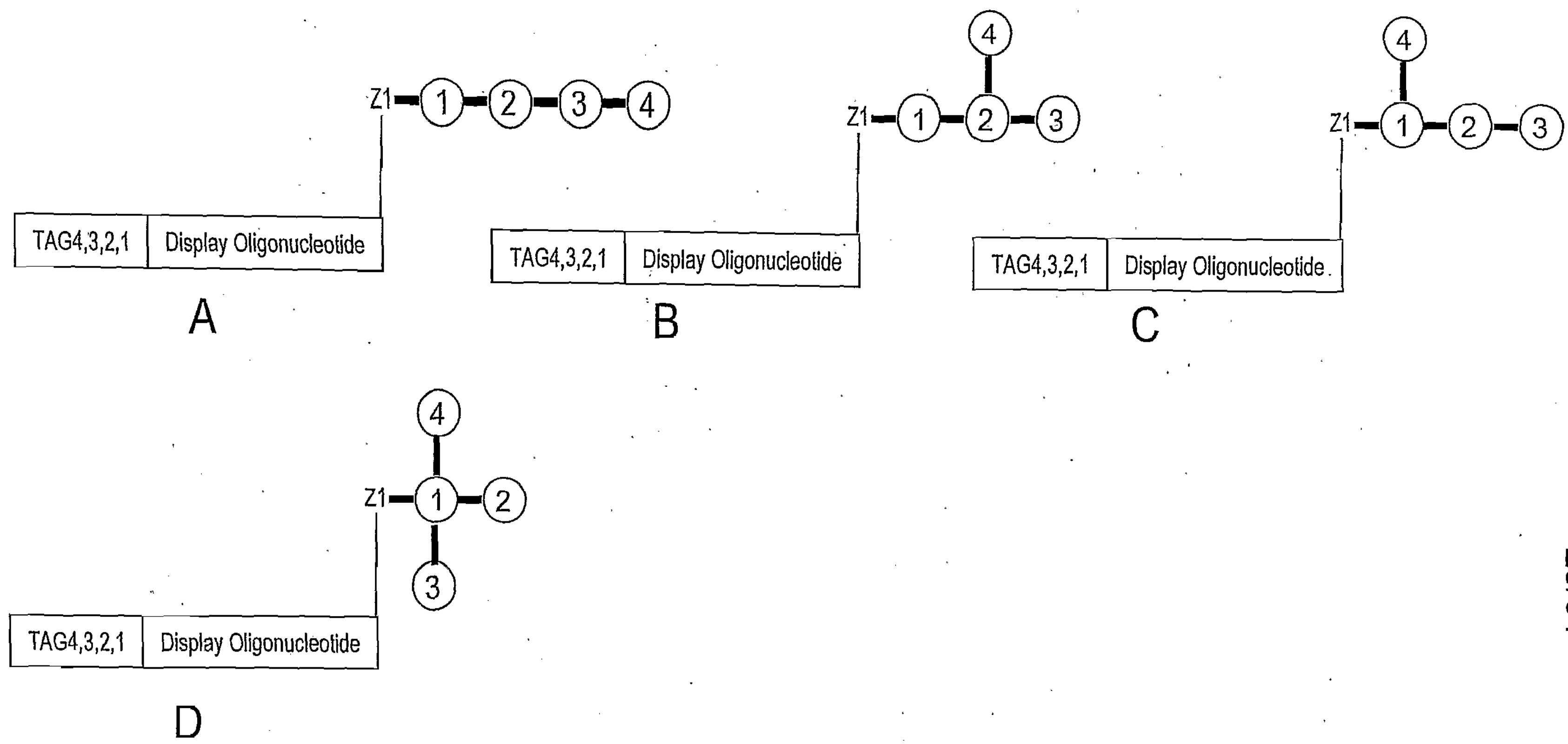




n = Denotes reactant n

= Denotes a product structure formed by the reaction of one or more chemical reaction sites and one or more reactants carrying one or more reactive groups. For example one or more covalent bonds formed between atoms of two or more reactants. Denotes in another embodiment one or covalent bonds formed between atoms of one or more reactants and one or more chemical reactive sites. Denotes in further embodiment a cyclic structure formed by the reaction between further reactive groups on two or more reactants.

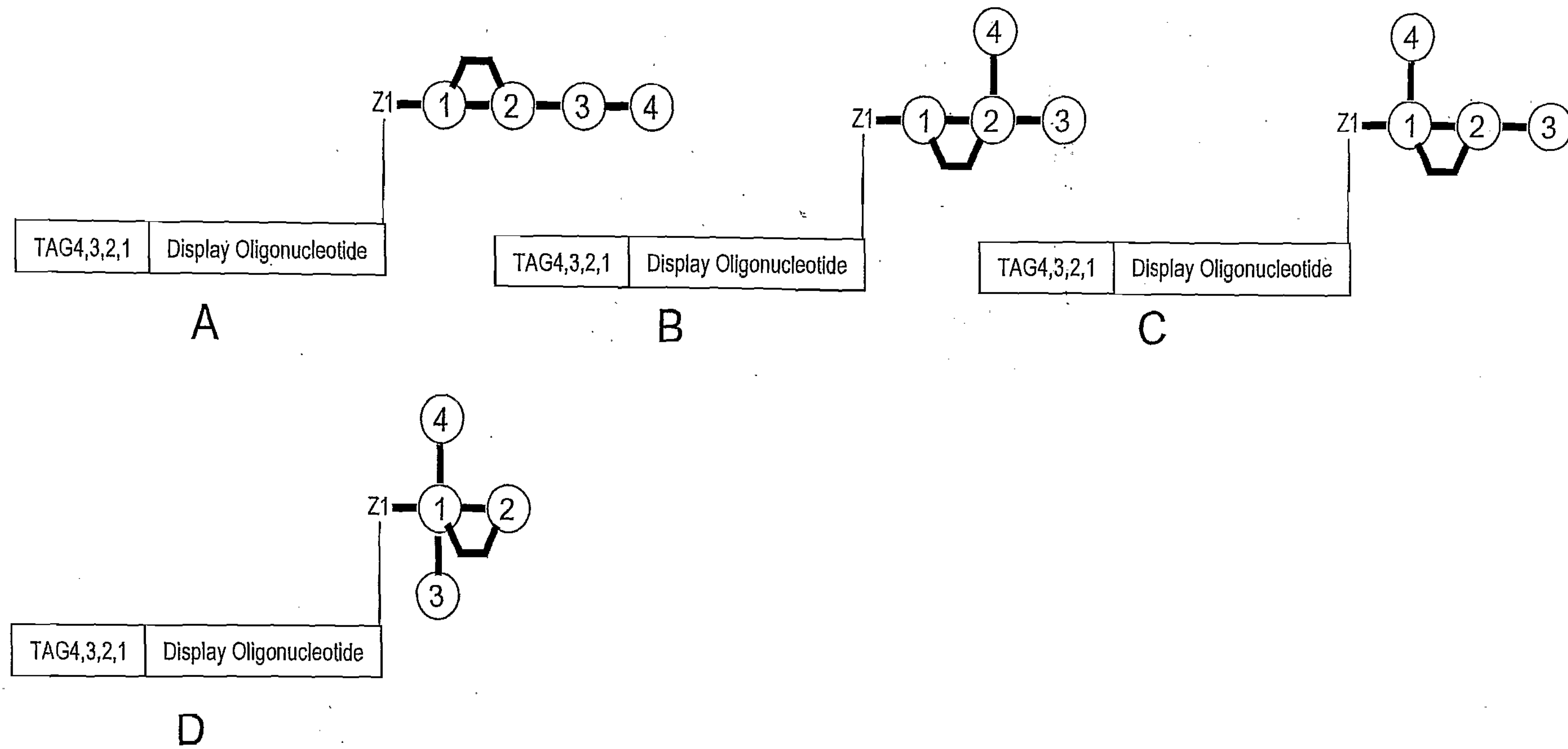
Fig. 28



(n) = Denotes reactant n

— = Denotes a product structure formed by the reaction of one or more chemical reaction sites and one or more reactants carrying one or more reactive groups. For example one or more covalent bonds formed between atoms of two or more reactants.
Denotes in another embodiment one or covalent bonds formed between atoms of one or more reactants and one or more chemical reactive sites.
Denotes in further embodiment a cyclic structure formed by the reaction between further reactive groups on two or more reactants.

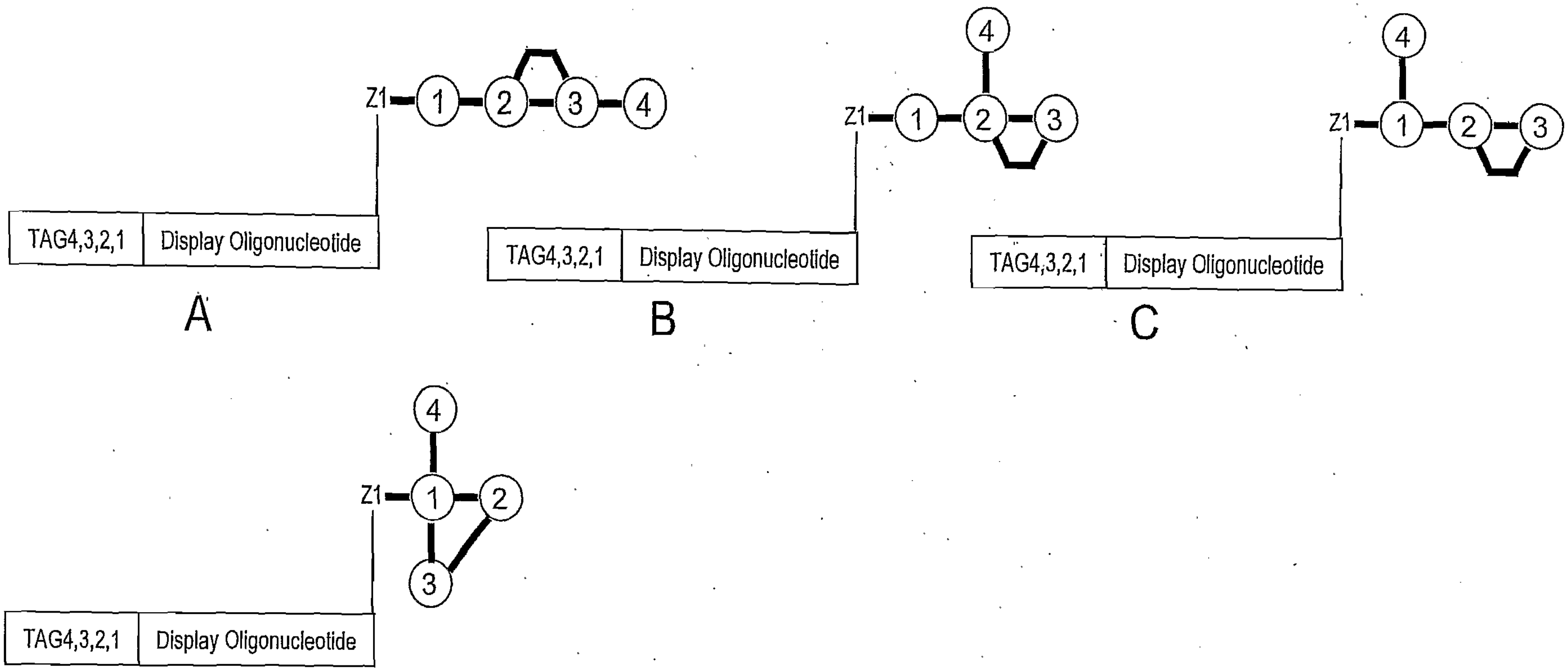
Fig. 29



n = Denotes reactant n

= Denotes a product structure formed by the reaction of one or more chemical reaction sites and one or more reactants carrying one or more reactive groups. For example one or more covalent bonds formed between atoms of two or more reactants.
Denotes in another embodiment one or covalent bonds formed between atoms of one or more reactants and one or more chemical reactive sites.
Denotes in further embodiment a cyclic structure formed by the reaction between further reactive groups on two or more reactants.

Fig. 30



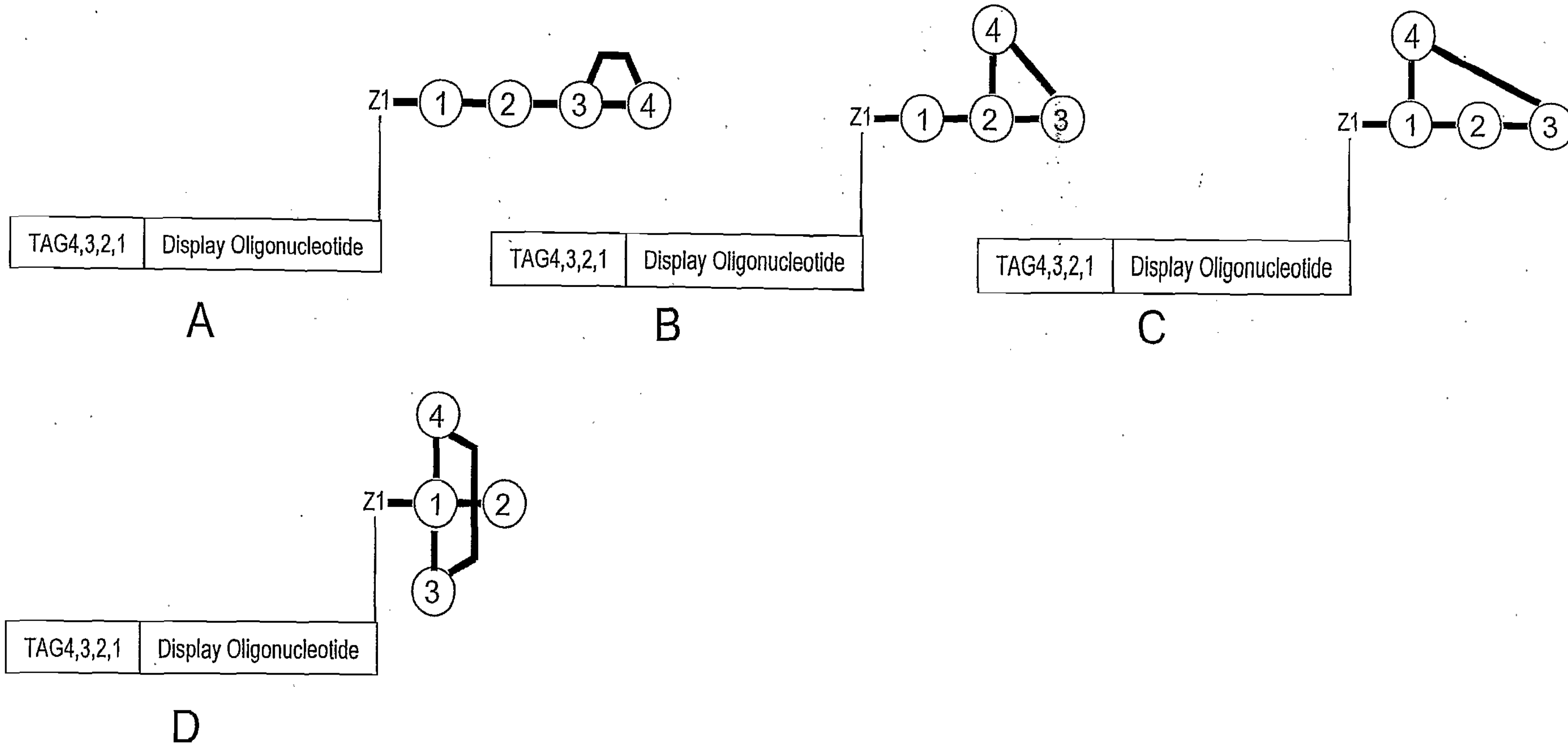
A B C

D

n = Denotes reactant n

= Denotes a product structure formed by the reaction of one or more chemical reaction sites and one or more reactants carrying one or more reactive groups. For example one or more covalent bonds formed between atoms of two or more reactants.
Denotes in another embodiment one or covalent bonds formed between atoms of one or more reactants and one or more chemical reactive sites.
Denotes in further embodiment a cyclic structure formed by the reaction between further reactive groups on two or more reactants.

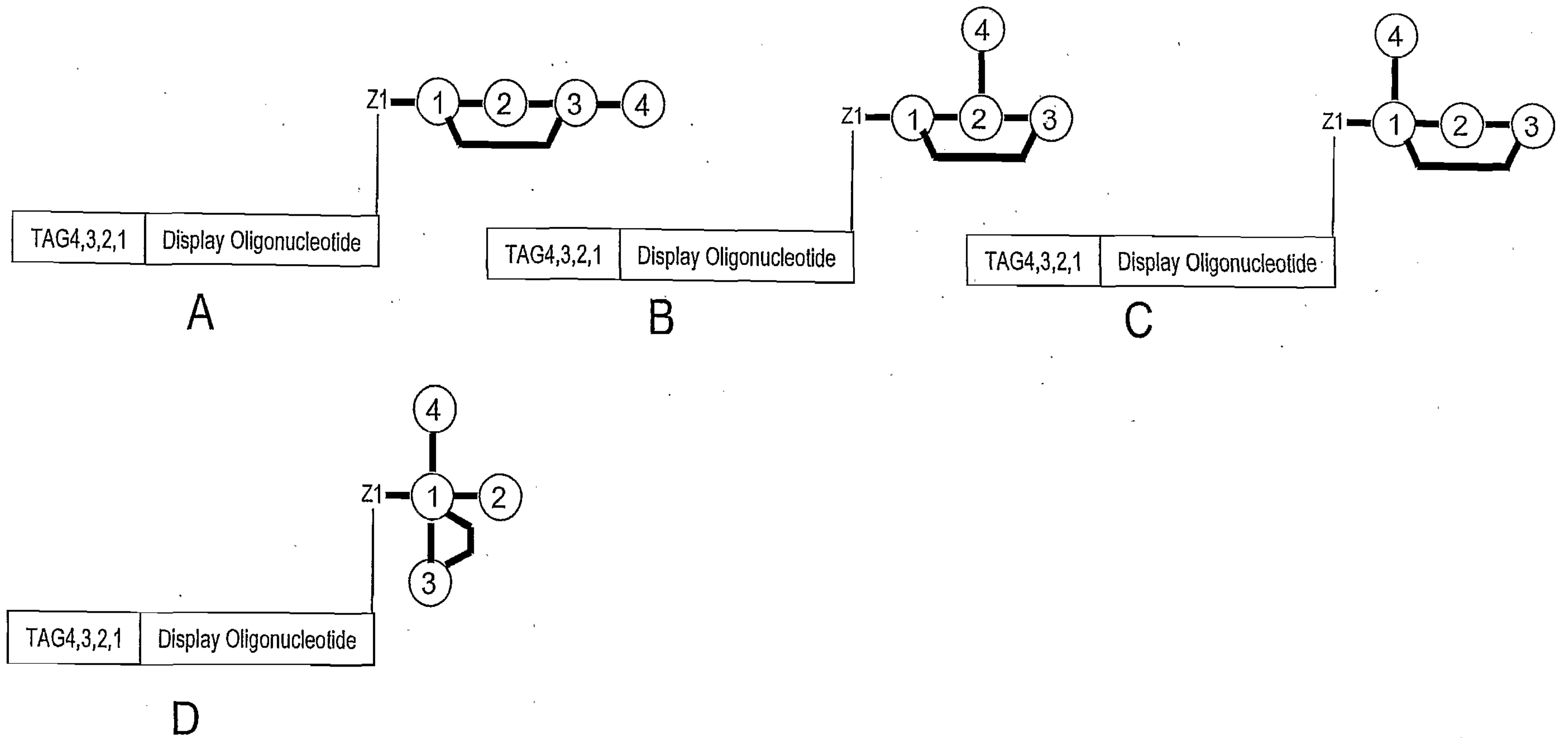
Fig. 31



n = Denotes reactant n

= Denotes a product structure formed by the reaction of one or more chemical reaction sites and one or more reactants carrying one or more reactive groups. For example one or more covalent bonds formed between atoms of two or more reactants.
Denotes in another embodiment one or covalent bonds formed between atoms of one or more reactants and one or more chemical reactive sites.
Denotes in further embodiment a cyclic structure formed by the reaction between further reactive groups on two or more reactants.

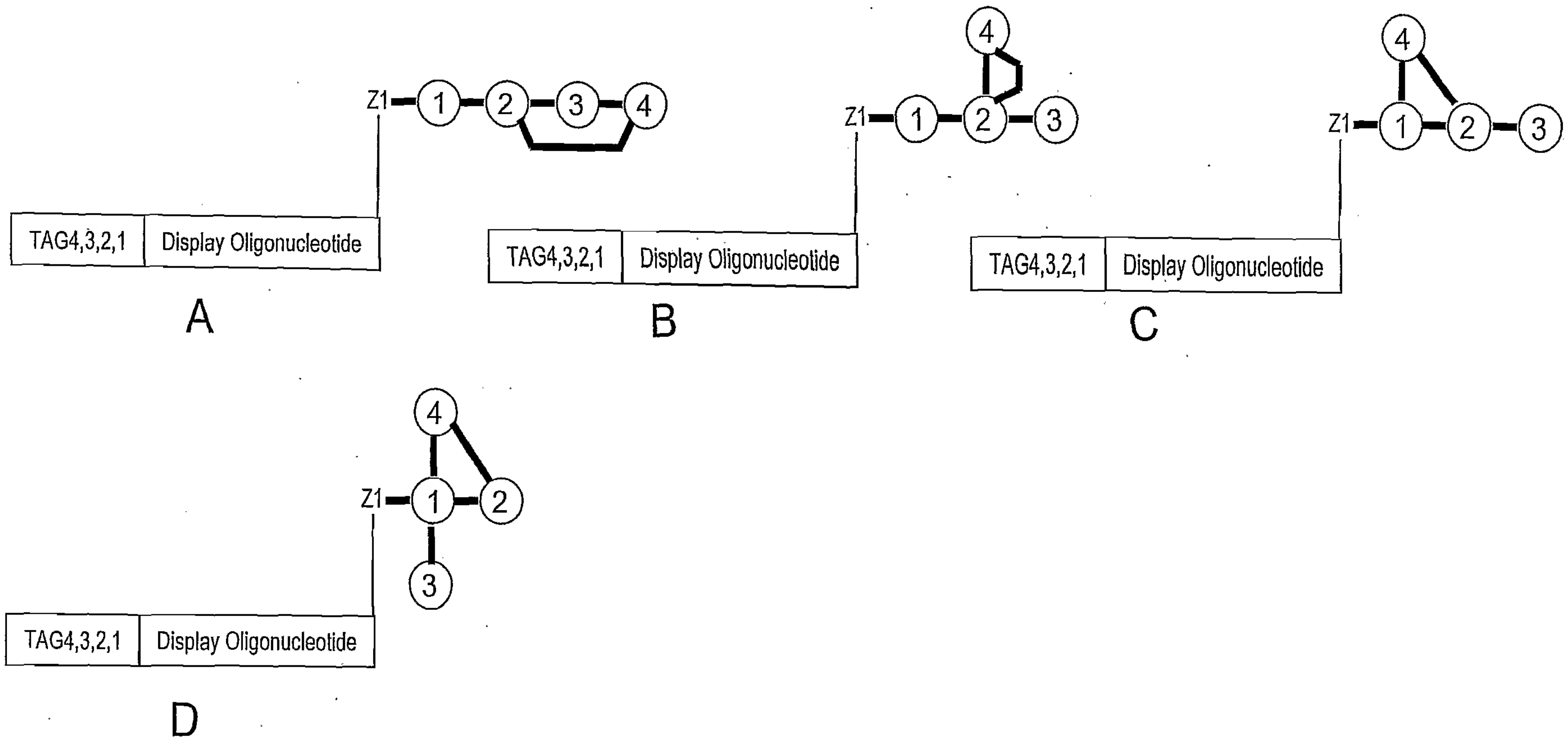
Fig. 32



n = Denotes reactant n

= Denotes a product structure formed by the reaction of one or more chemical reaction sites and one or more reactants carrying one or more reactive groups. For example one or more covalent bonds formed between atoms of two or more reactants.
Denotes in another embodiment one or covalent bonds formed between atoms of one or more reactants and one or more chemical reactive sites.
Denotes in further embodiment a cyclic structure formed by the reaction between further reactive groups on two or more reactants.

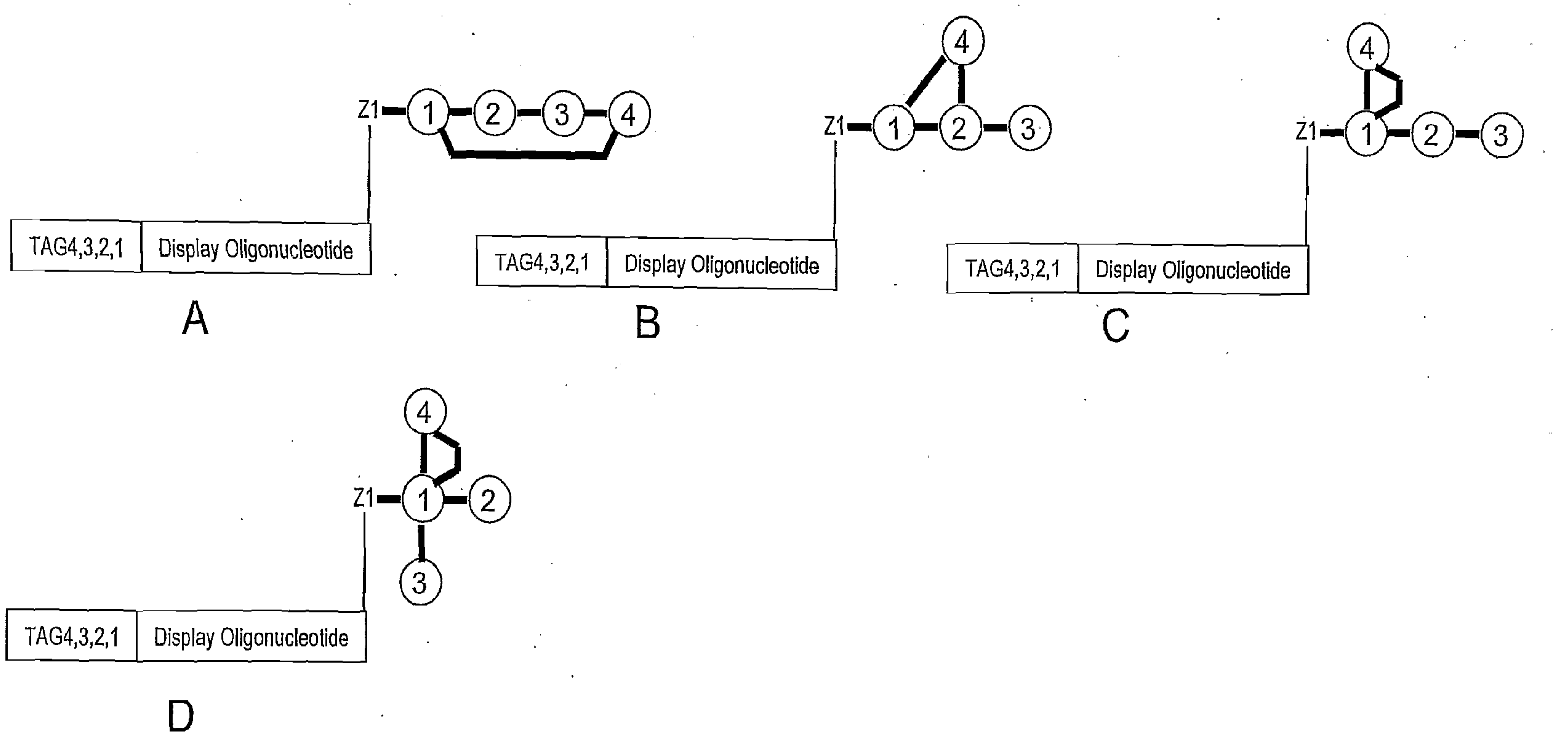
Fig. 33



(n) = Denotes reactant n

= Denotes a product structure formed by the reaction of one or more chemical reaction sites and one or more reactants carrying one or more reactive groups. For example one or more covalent bonds formed between atoms of two or more reactants.
Denotes in another embodiment one or covalent bonds formed between atoms of one or more reactants and one or more chemical reactive sites.
Denotes in further embodiment a cyclic structure formed by the reaction between further reactive groups on two or more reactants.

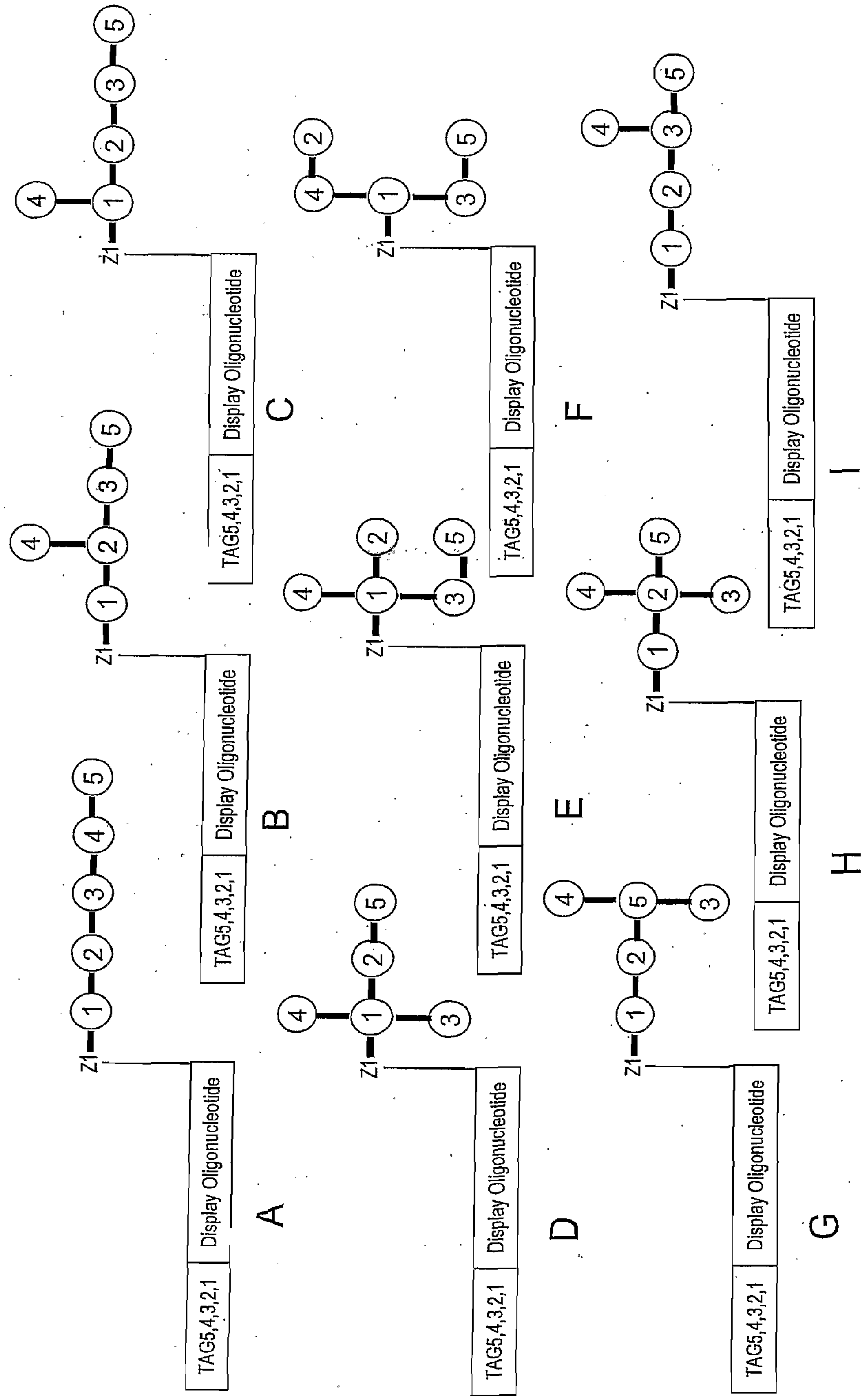
Fig. 34



n = Denotes reactant n

= Denotes a product structure formed by the reaction of one or more chemical reaction sites and one or more reactants carrying one or more reactive groups. For example one or more covalent bonds formed between atoms of two or more reactants.
Denotes in another embodiment one or covalent bonds formed between atoms of one or more reactants and one or more chemical reactive sites.
Denotes in further embodiment a cyclic structure formed by the reaction between further reactive groups on two or more reactants.

Fig. 35



(n) = Denotes reactant n

▬ = Denotes a product structure formed by the reaction of one or more chemical reaction sites and one or more reactants carrying one or more reactive groups. For example one or more covalent bonds formed between atoms of two or more reactants.
Denotes in another embodiment one or covalent bonds formed between atoms of one or more reactants and one or more chemical reactive sites.
Denotes in further embodiment a cyclic structure formed by the reaction between further reactive groups on two or more reactants.

Fig. 36

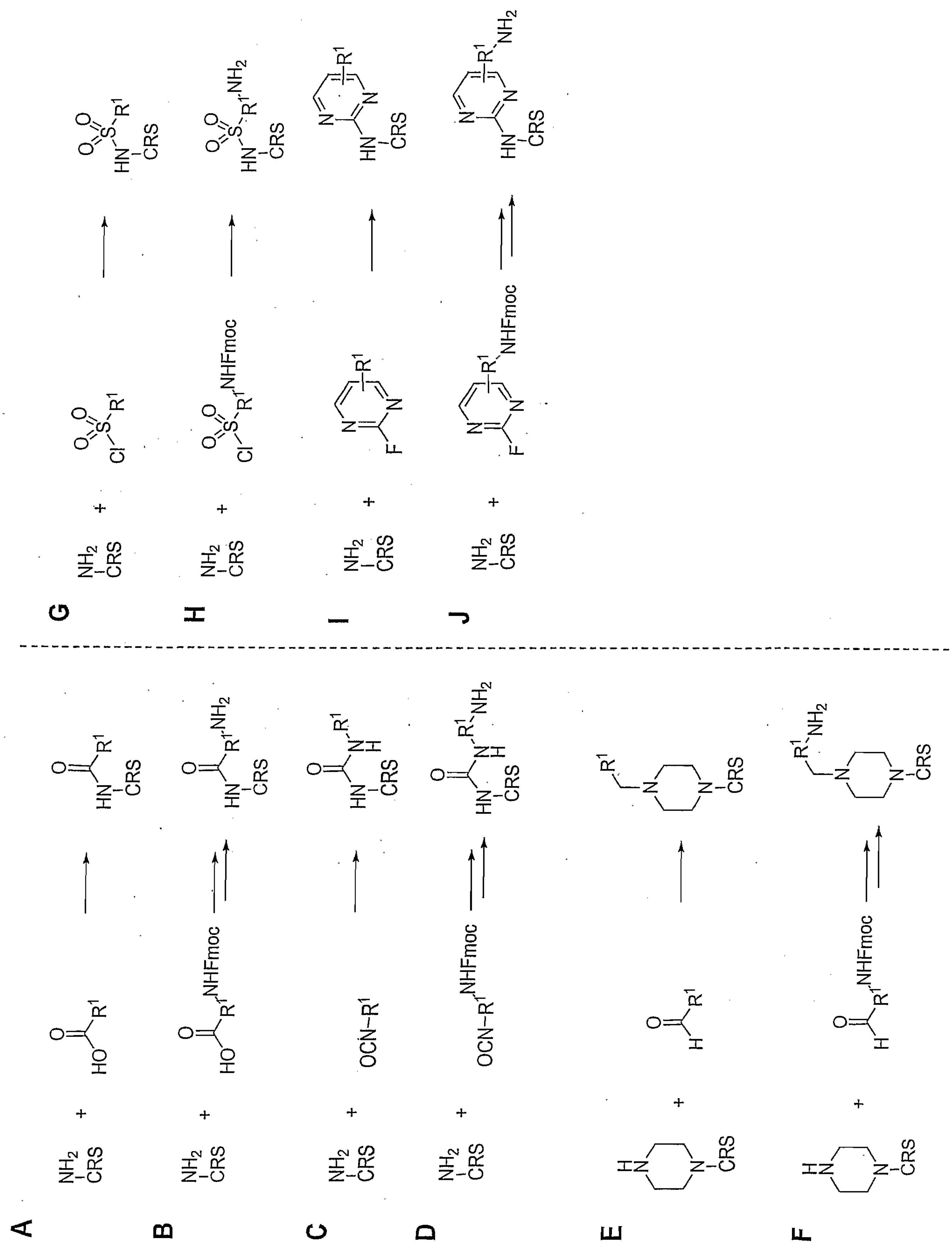


Fig. 37

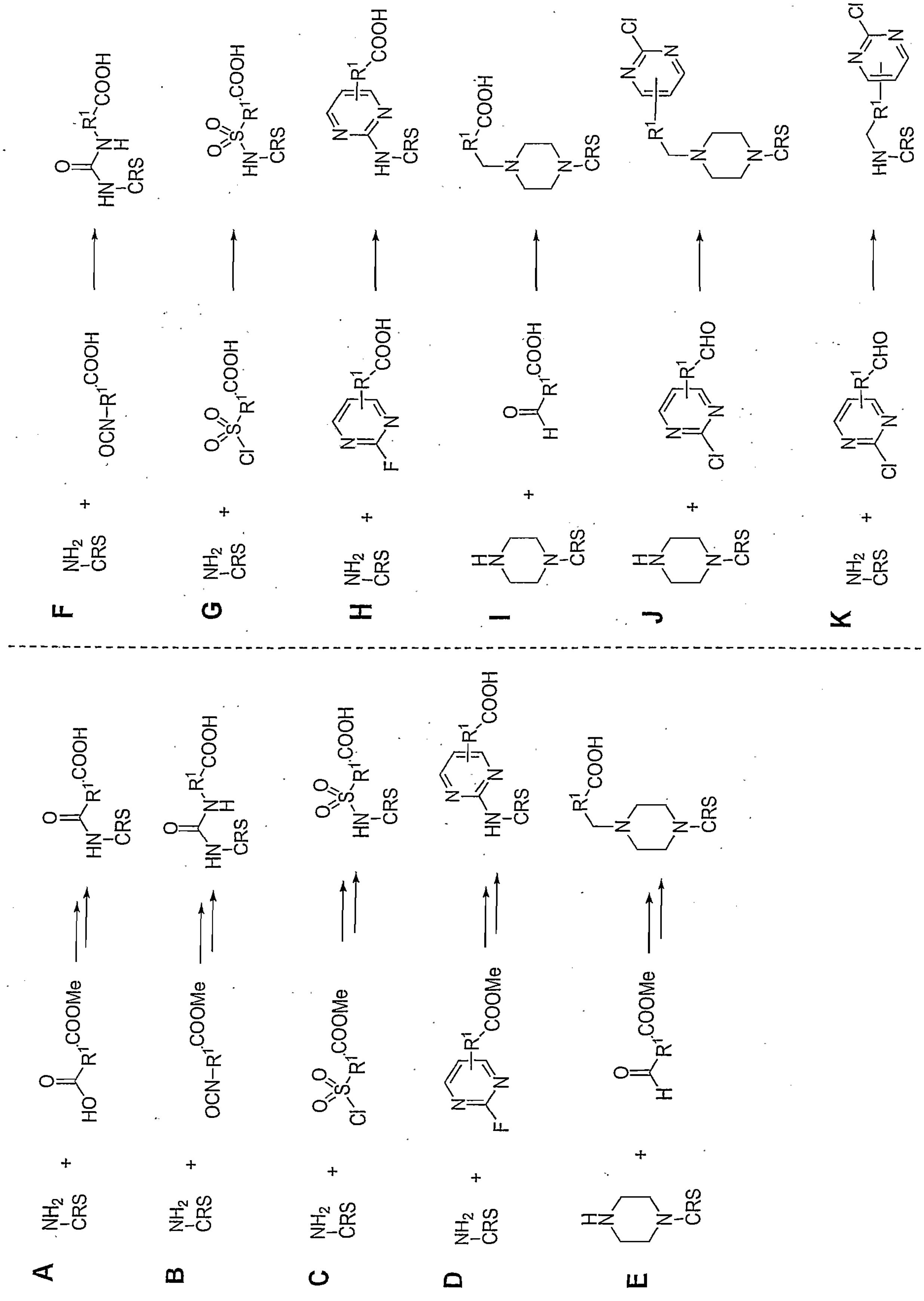


Fig. 38

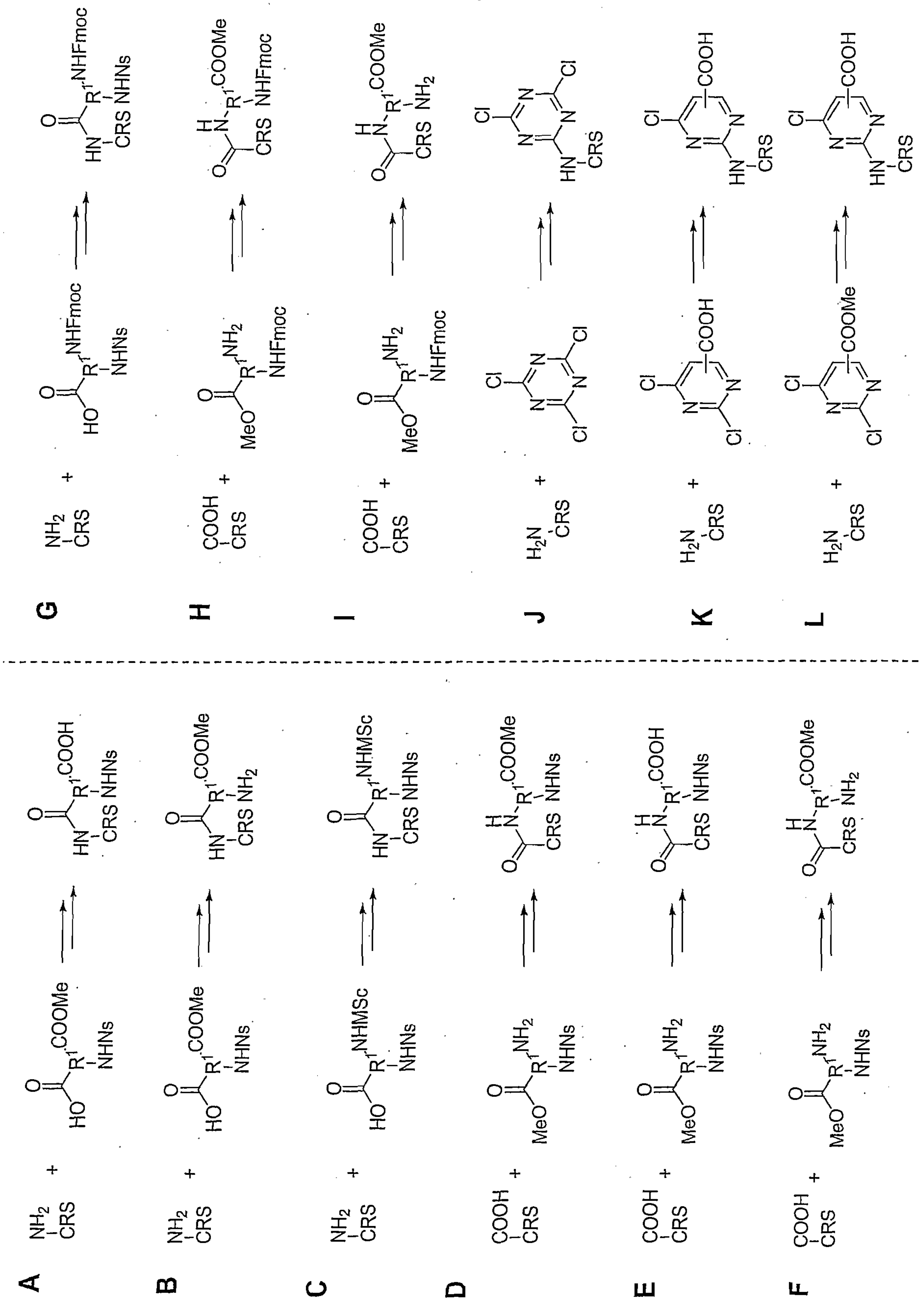


Fig. 39

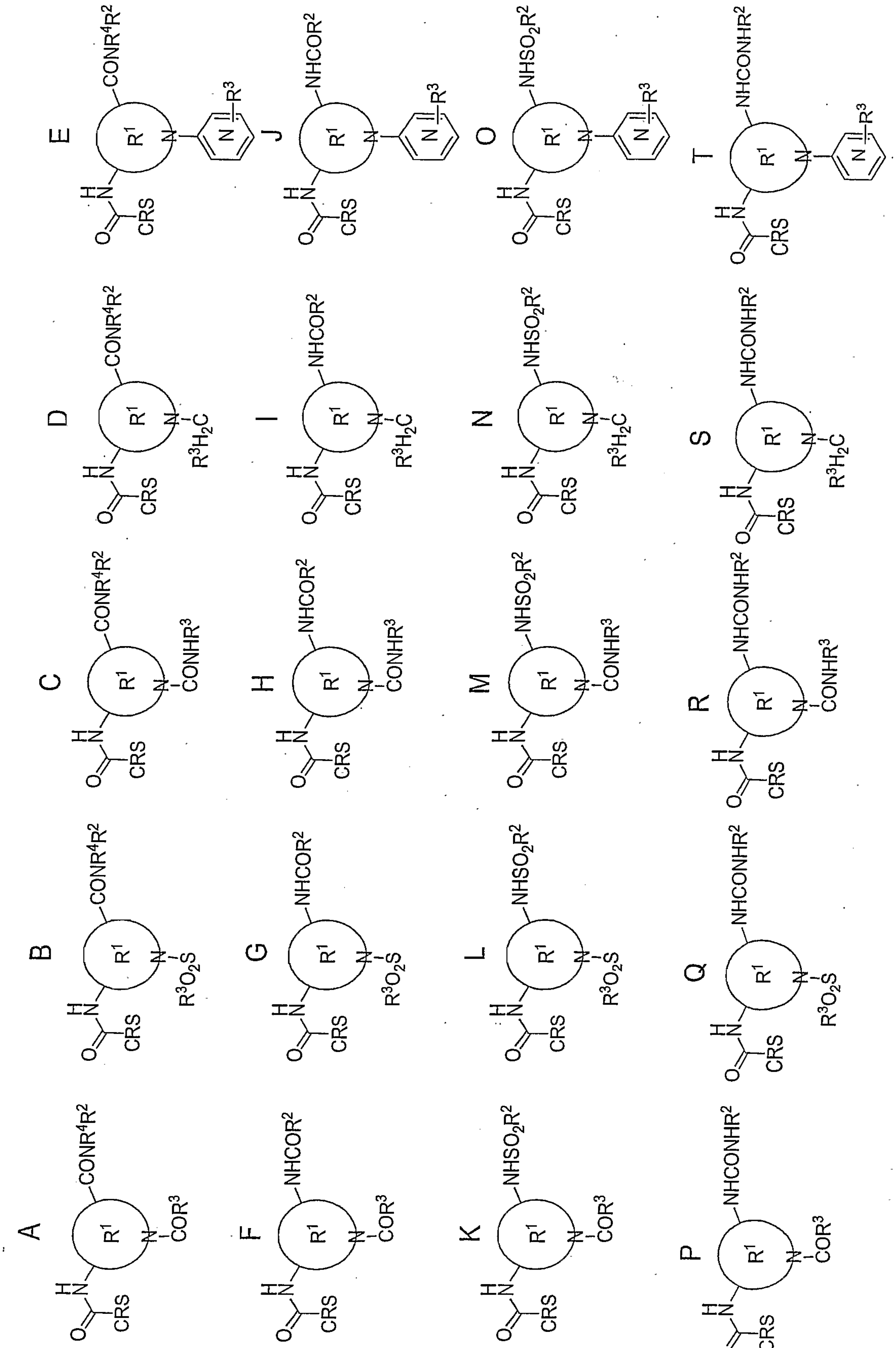


Fig. 40

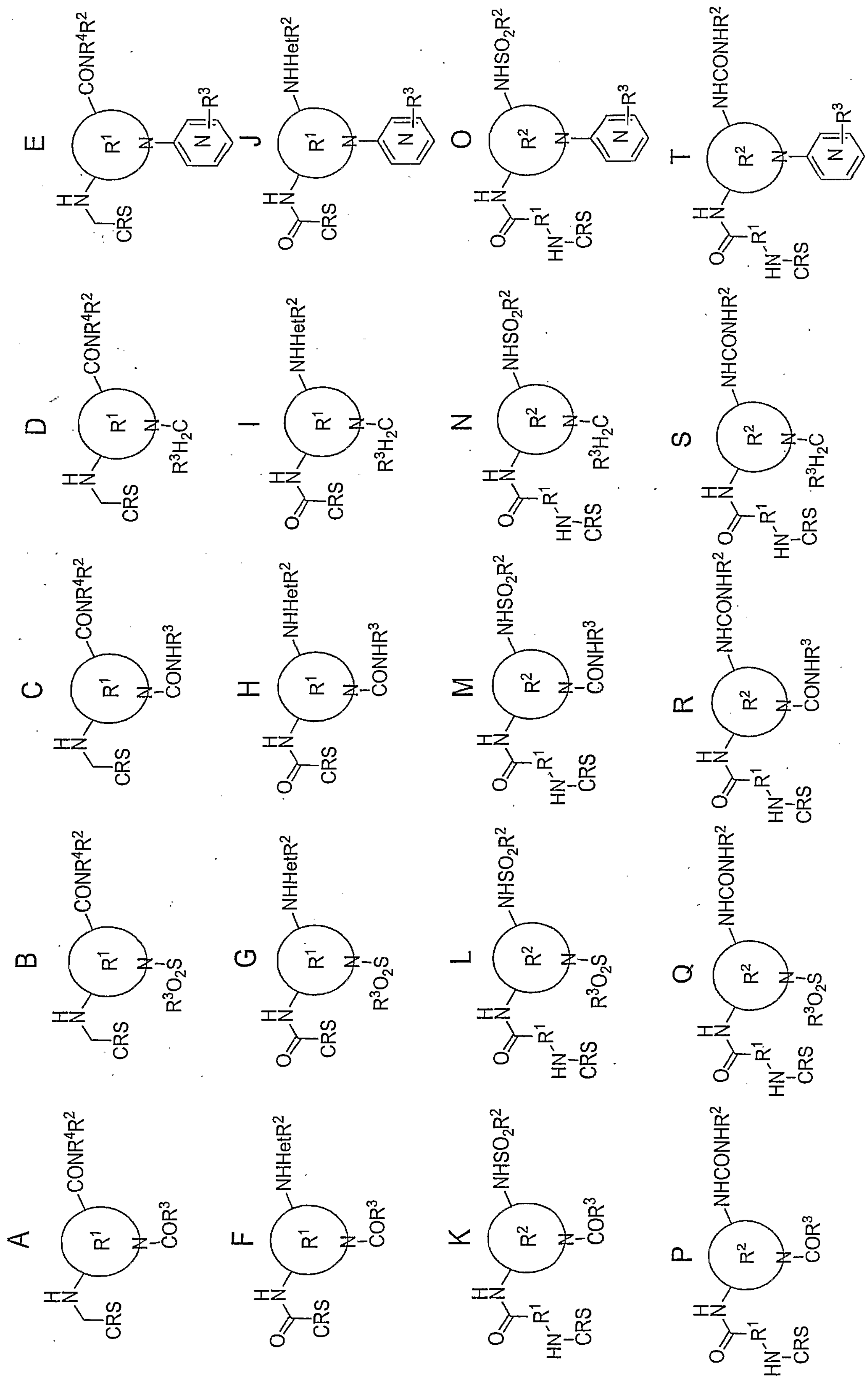


Fig. 41

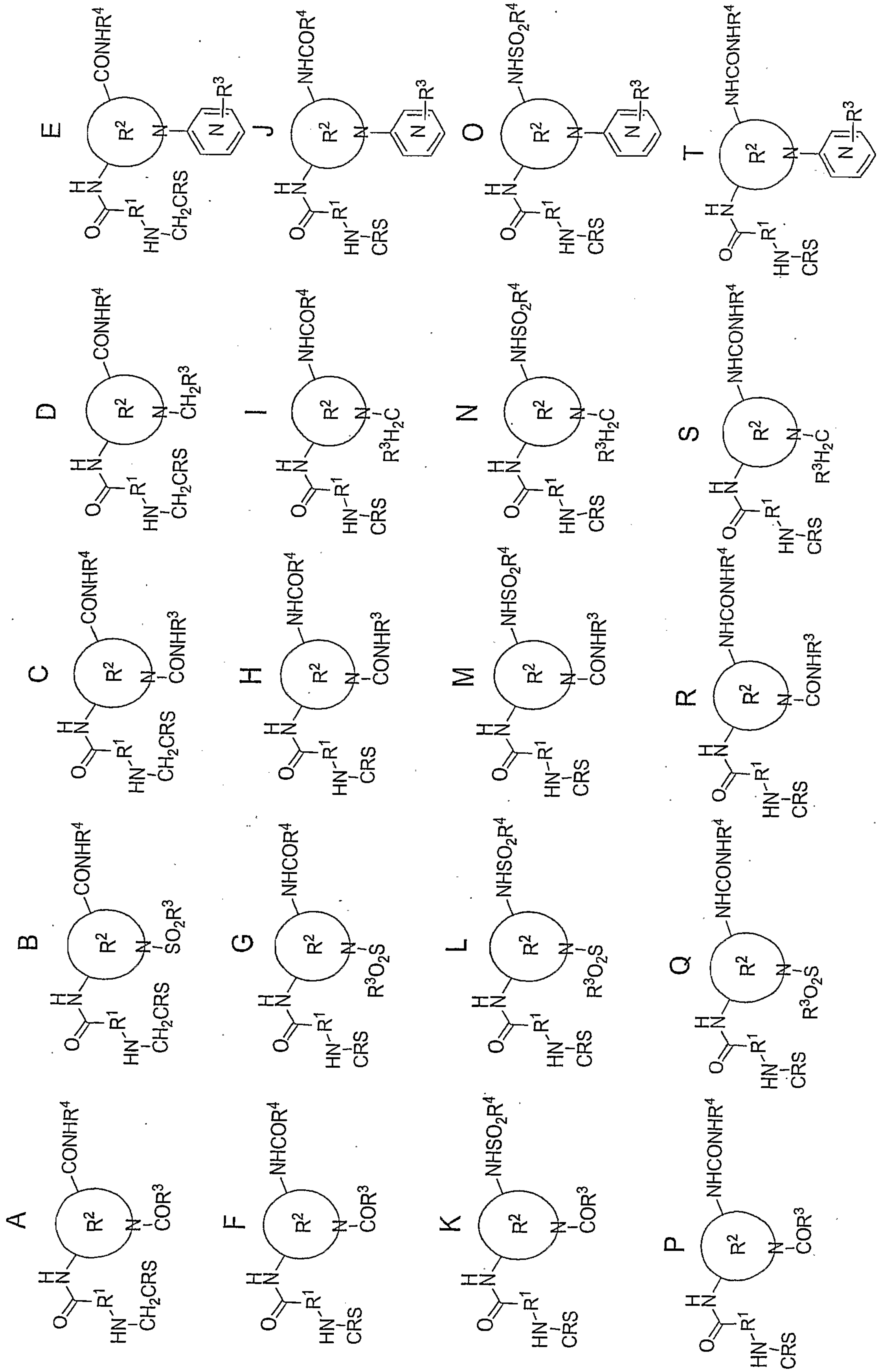


Fig. 42

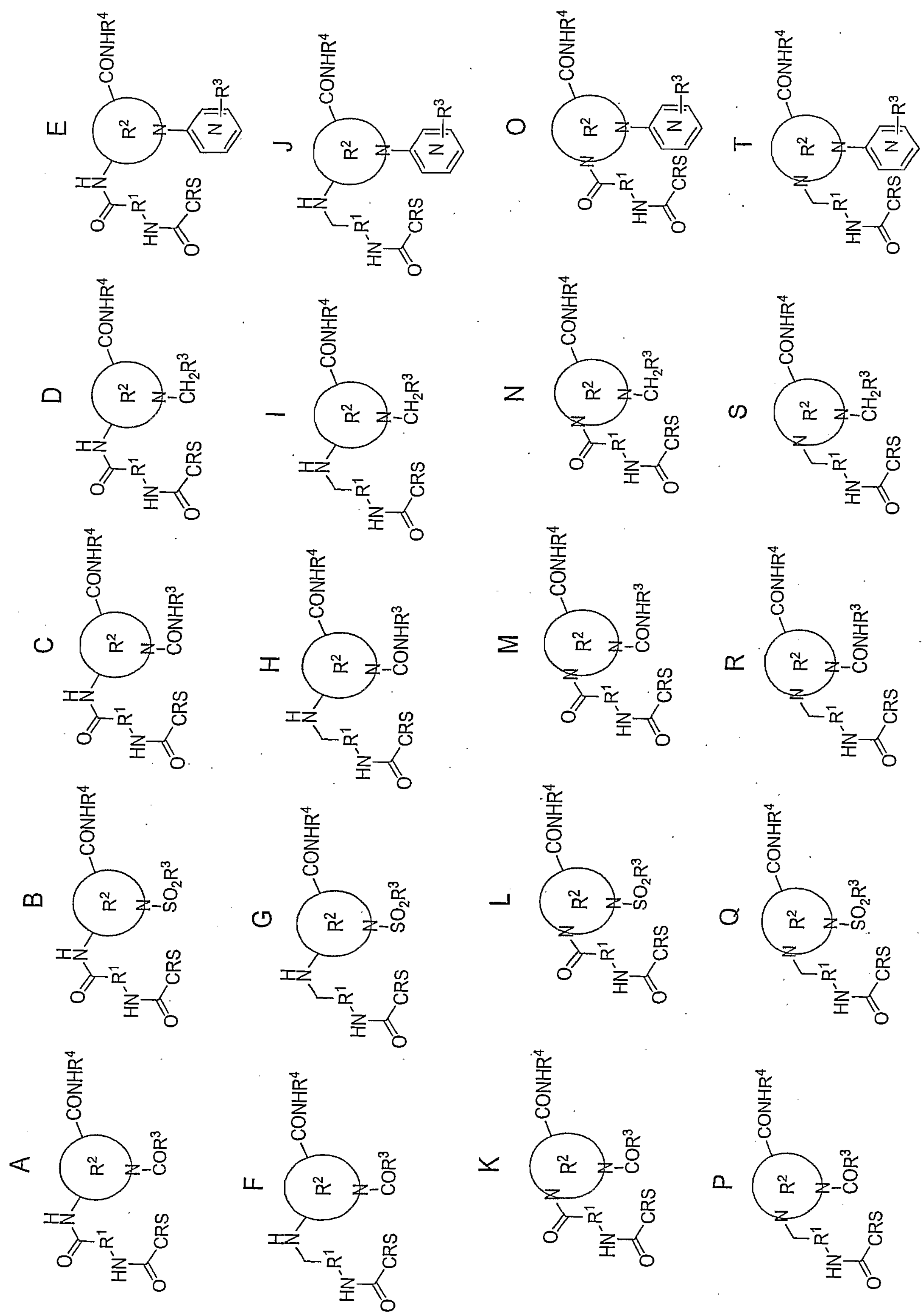


Fig. 43

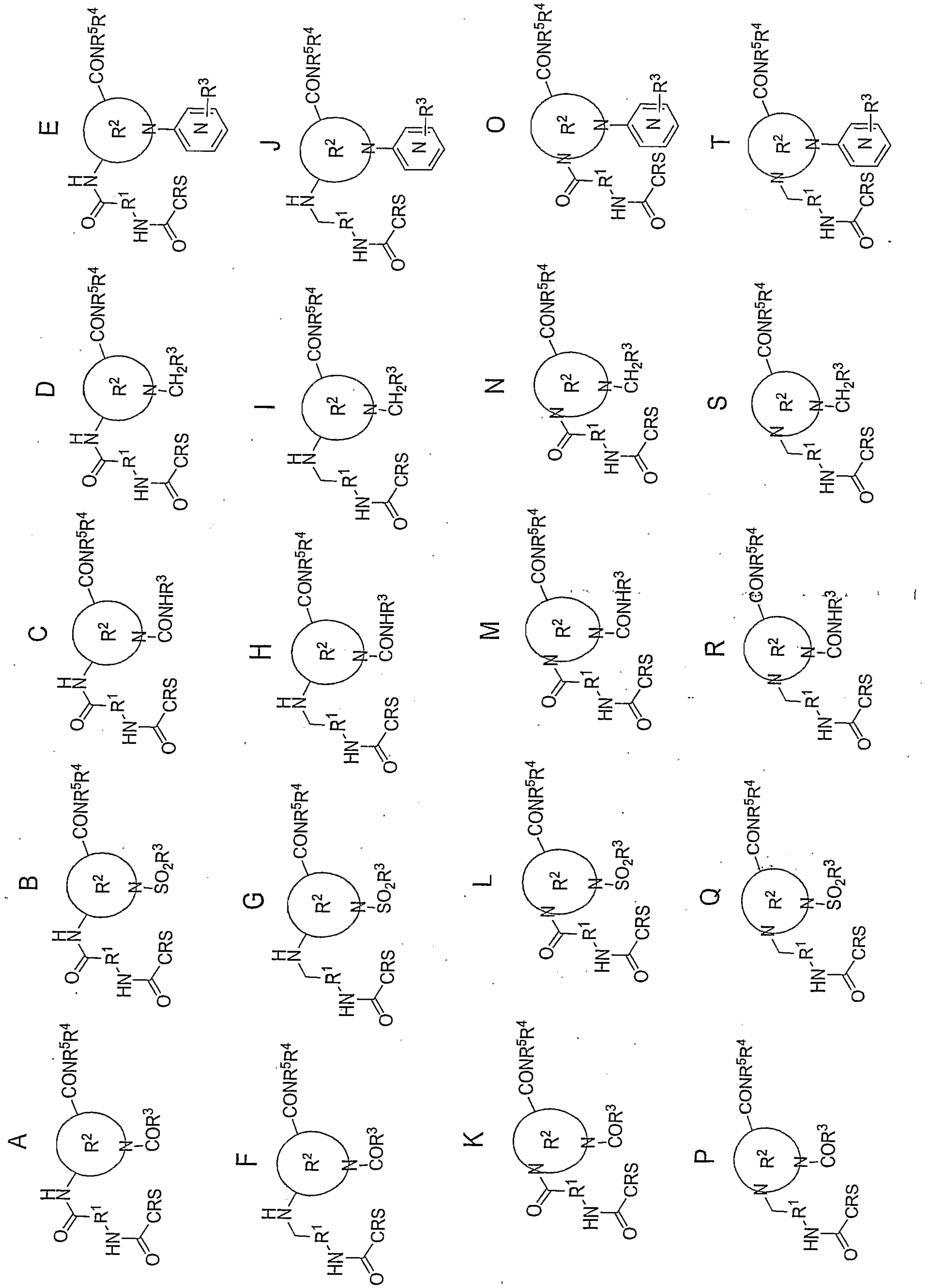


Fig. 44

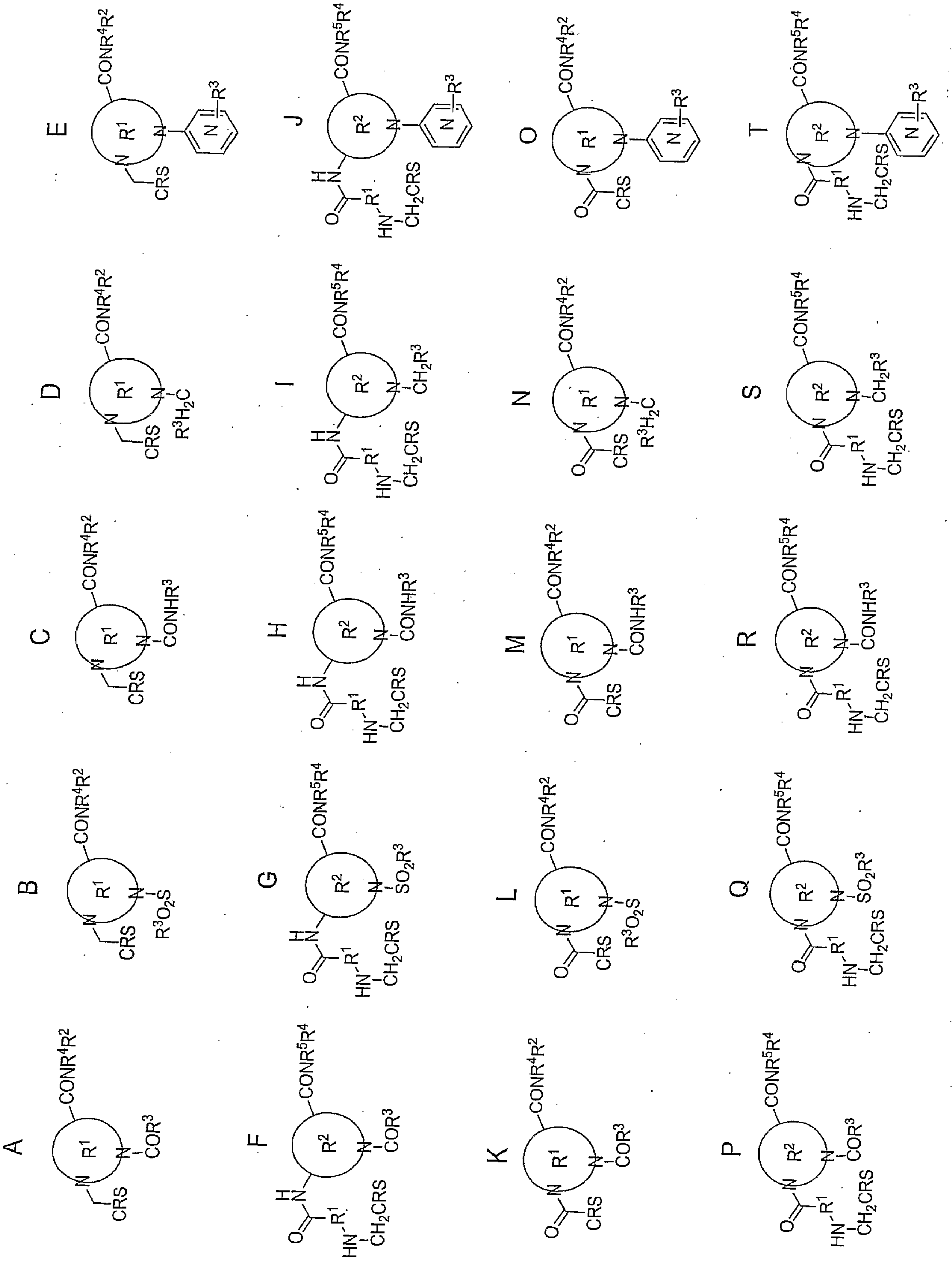


Fig. 45

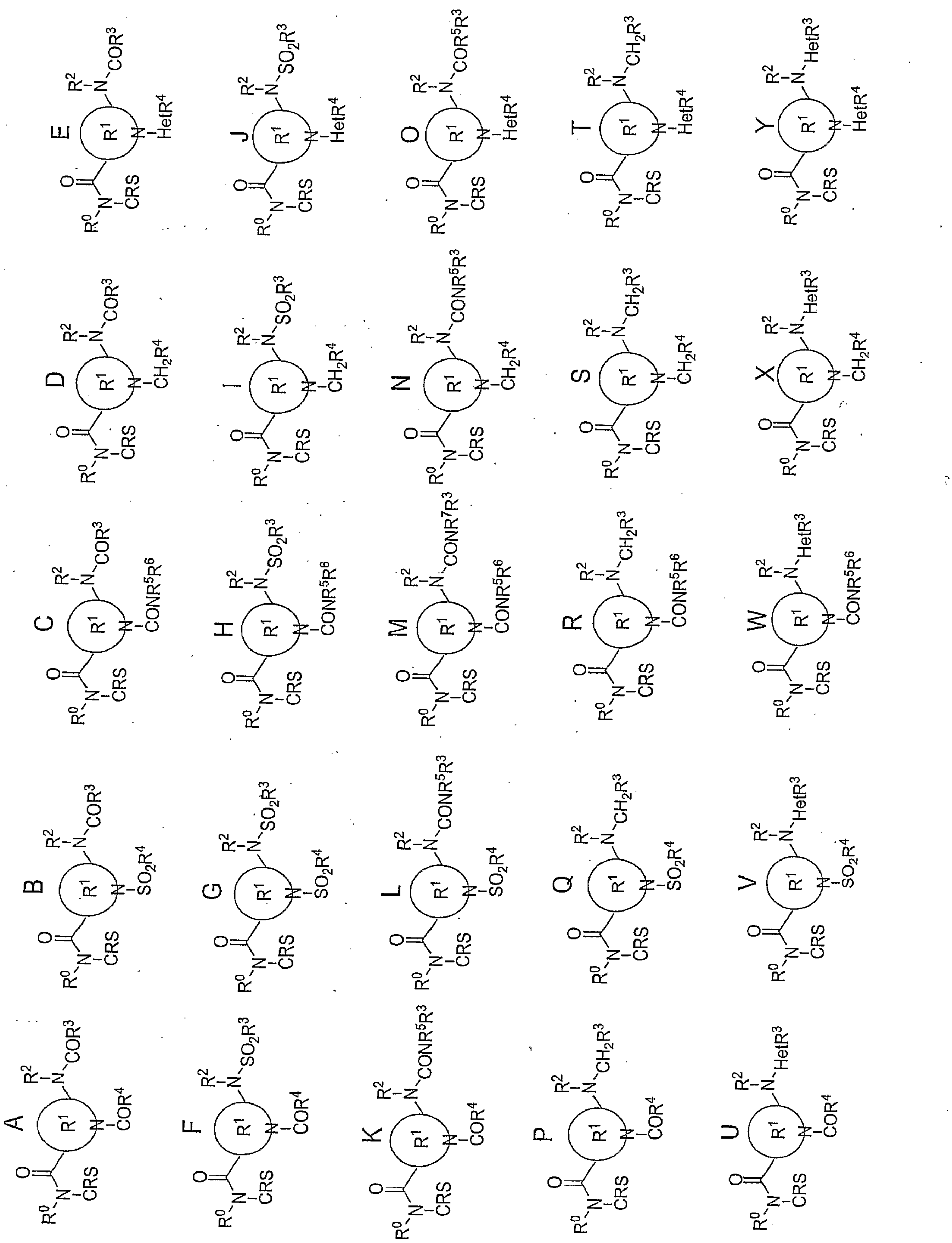


Fig. 46

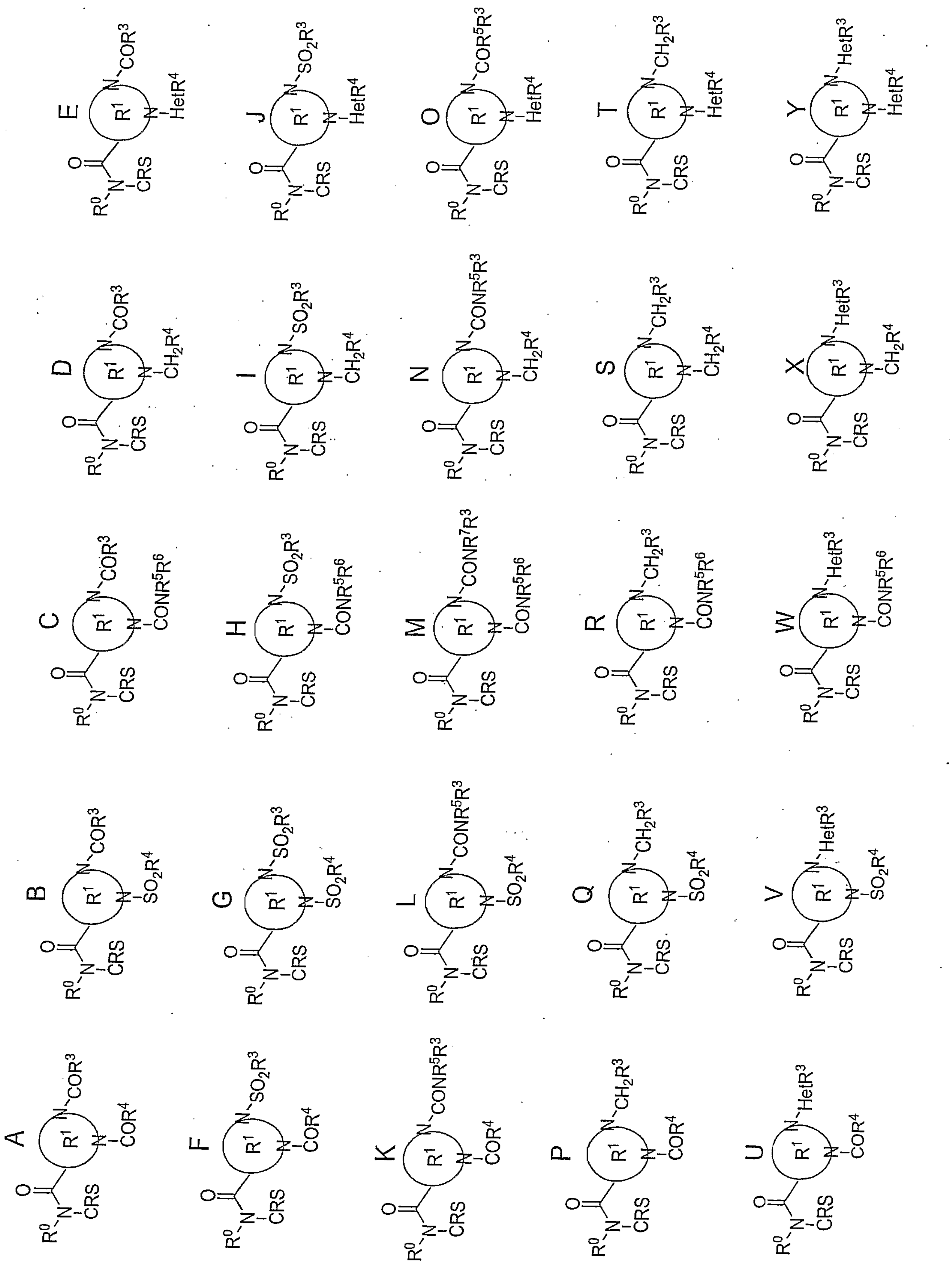


Fig. 47

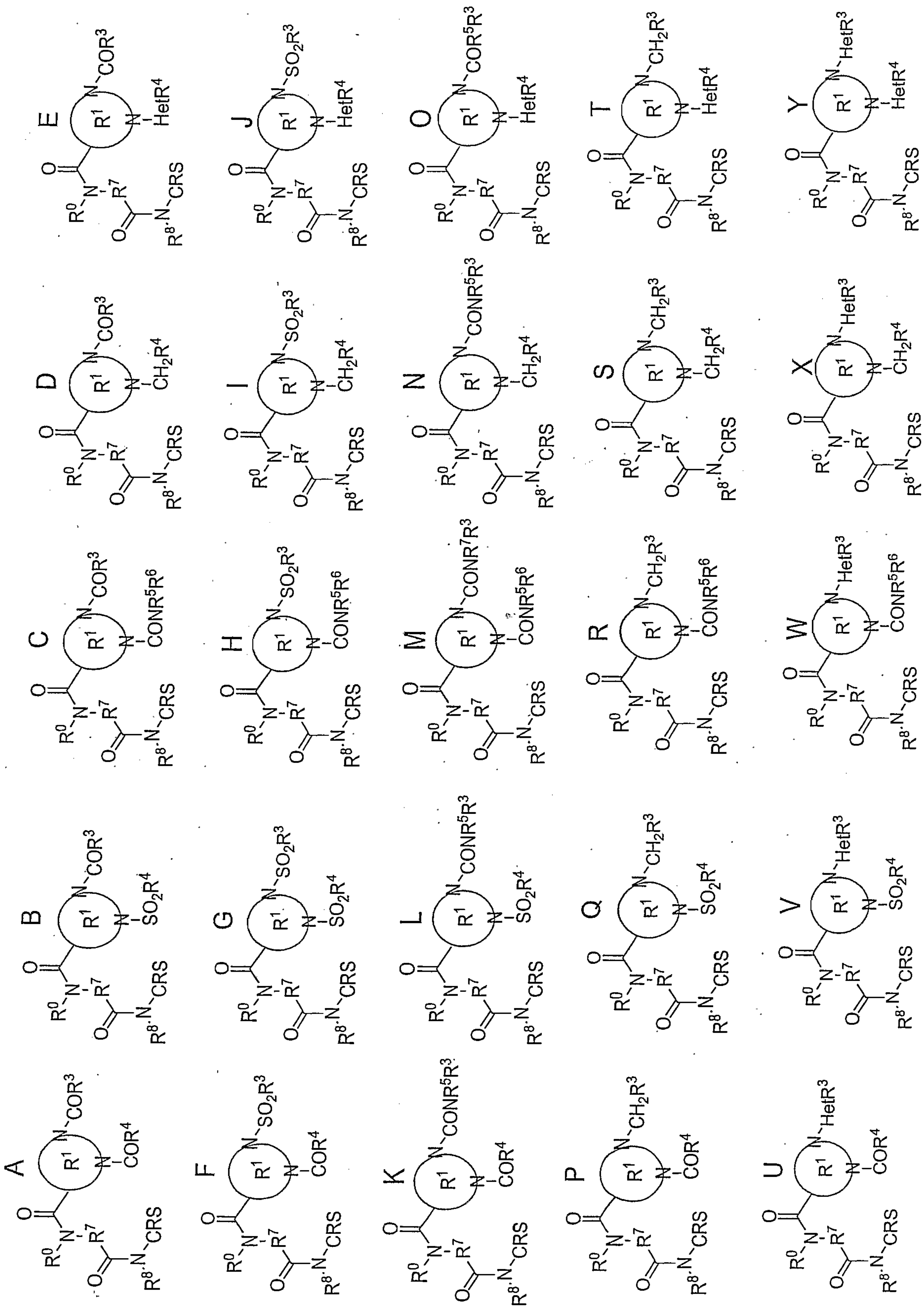


Fig. 48

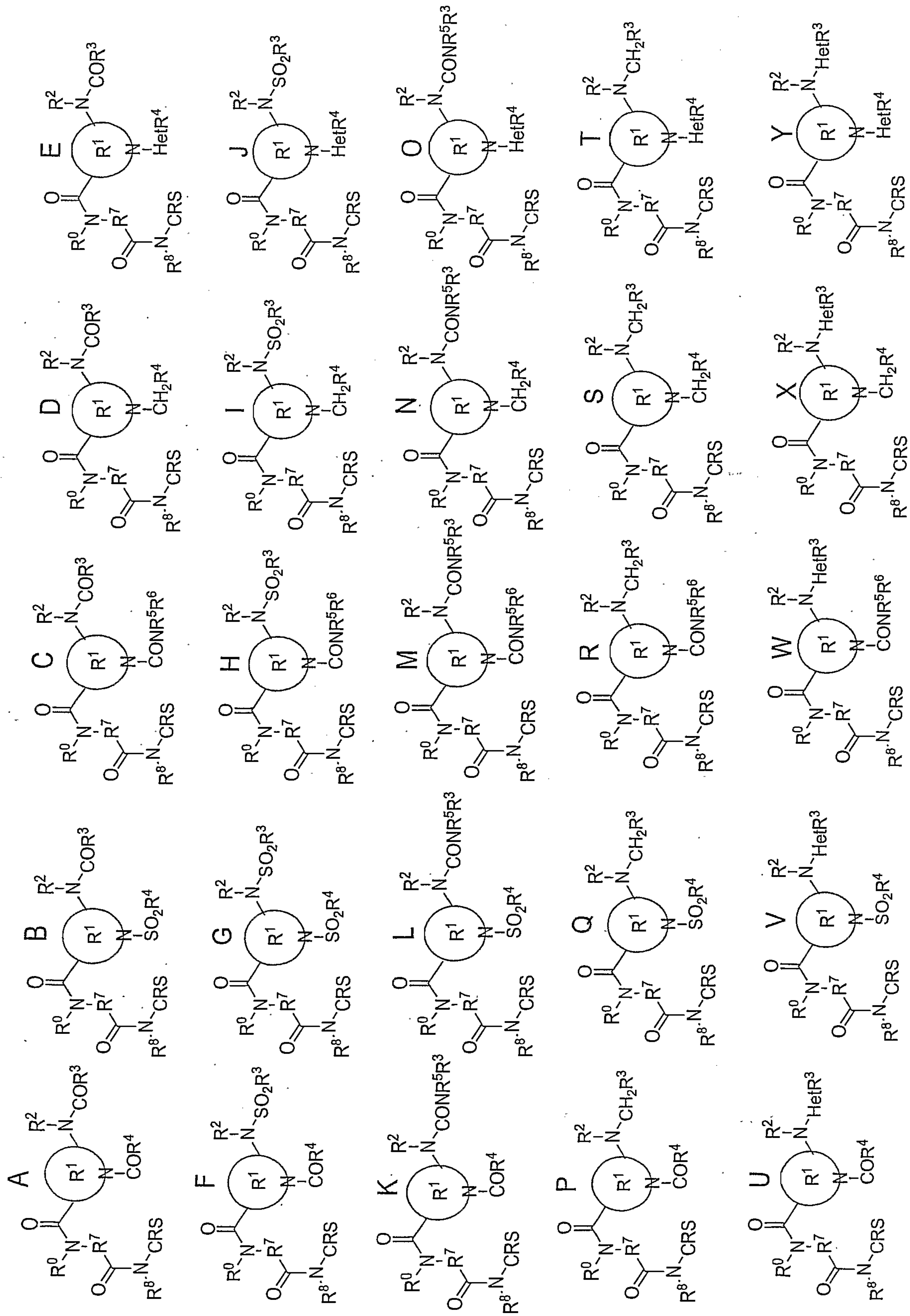


Fig. 49

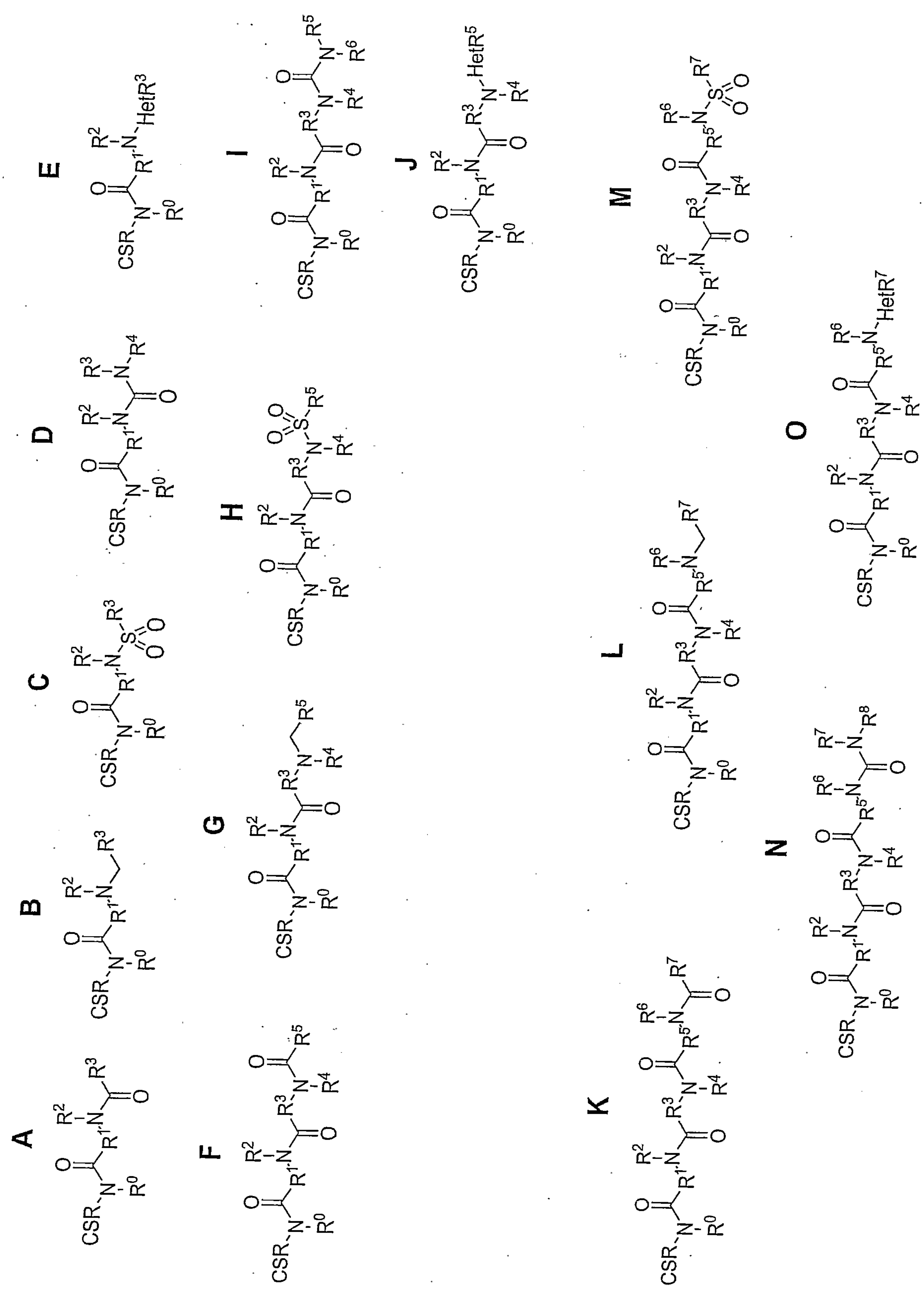


Fig. 50

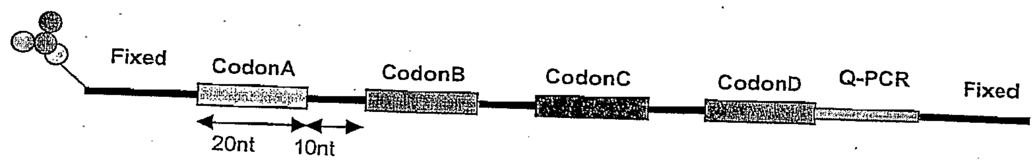
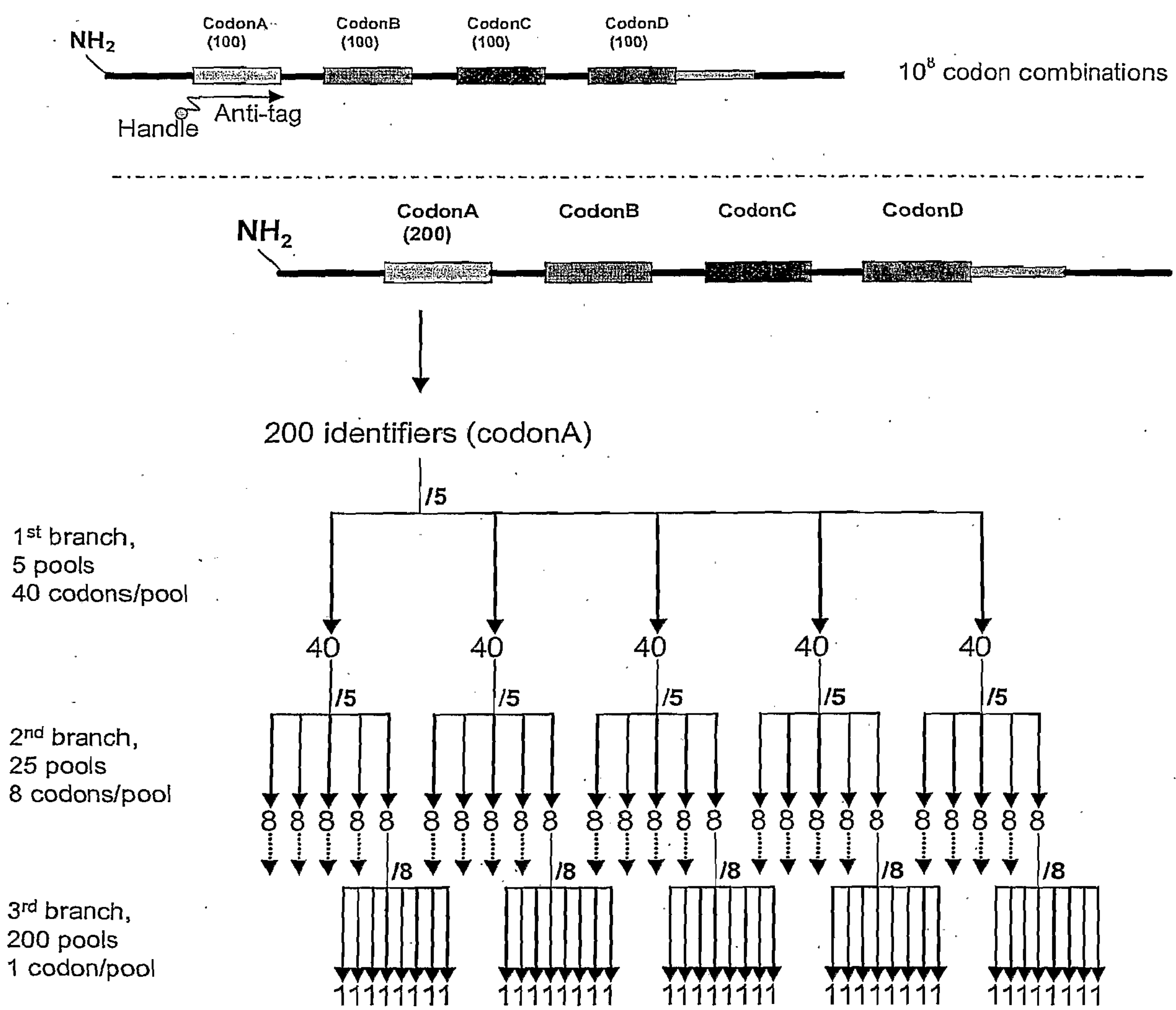


Fig. 51



NH2
CodonA (100)
CodonB (100)
CodonC (100)
CodonD (100)
10^8 codon combinations
Handle
Anti-tag
NH2
CodonA (200)
CodonB
CodonC
CodonD
200 identifiers (codonA)
1st branch, 5 pools 40 codons/pool
2nd branch, 25 pools 8 codons/pool
3rd branch, 200 pools 1 codon/pool
/5
40
/8
8
1

Fig. 52

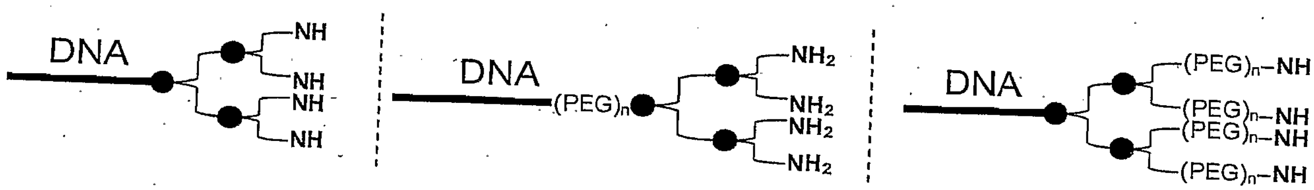

DNA
NH
NH
NH
NH
DNA
(PEG)n
NH2
NH2
NH2
NH2
DNA
(PEG)n–NH
(PEG)n–NH
(PEG)n–NH
(PEG)n–NH

Fig. 53

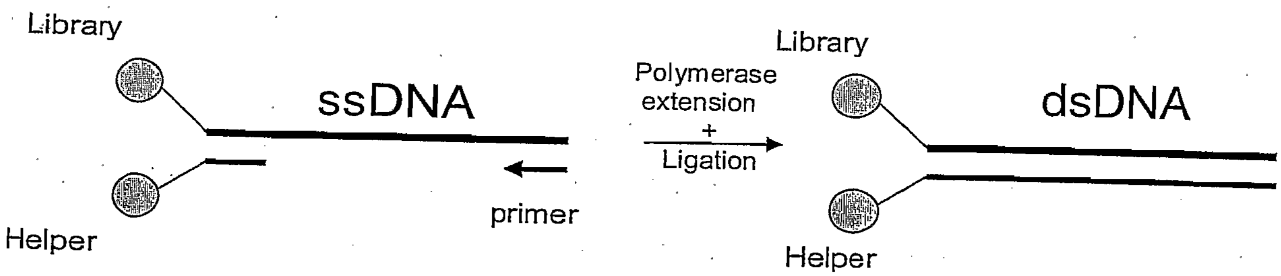
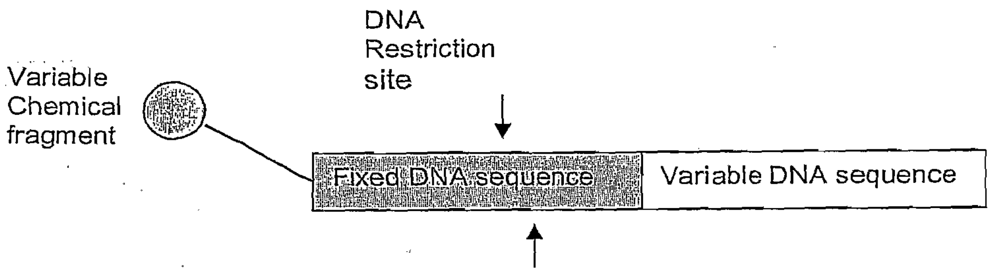

Library
ssDNA
Helper
primer
Polymerase
extension
+
Ligation
Library
dsDNA
Helper

Fig. 54



Step 1:
Following parallel chemical reactions, a sample or a pool of samples from n reactions comprising a total of ~ 100 pmol of DNA is subtracted for ES-MS analysis.

Step2:
Add 500 pmol of Biotinylated antisense DNA complementary to the fixed sequence and add EcoRI Restriction buffer [90 mM HCl, 10 mM MgCl2, 50 mM NaCl, pH7.5] in a total volume of 100 ul.
Denature sample at 90 oC for 2 min and cool sample to 37oC. Add 20 units of EcoRI and incubate for a minimum of 2 hours.

Step3:
Prepare Streptavidine beads by washing 50 ul of SA-bead
slurry (Amersham) with 1 ml of 25 mM NH_4-acetate (pH 7.25) X 3 and transfer the slurry to a Spin-X column with cellulose-acetate filter (Corning cat#8160/8161).
Add the *EcoRI* restriction sample and incubate at 30 oC for 15 min. Wash 3 times with 500 ul of NH_4-acetate buffer

Step4
The 12 nt DNA seqment with attached chemical building block(s)is eluted by addition of 50 ul of H2O at 80 oC for 30 sec followed removal of SA-beads using immediate spin-filtration.

Step5
The sample is dried down and redissolved in 50 ul ES-MS buffer Containing 25 mM imidazole/25mM piperidine in a 50:50 mixture of H2O/Acetonitril before applying the sample to the ES-MS for analysis

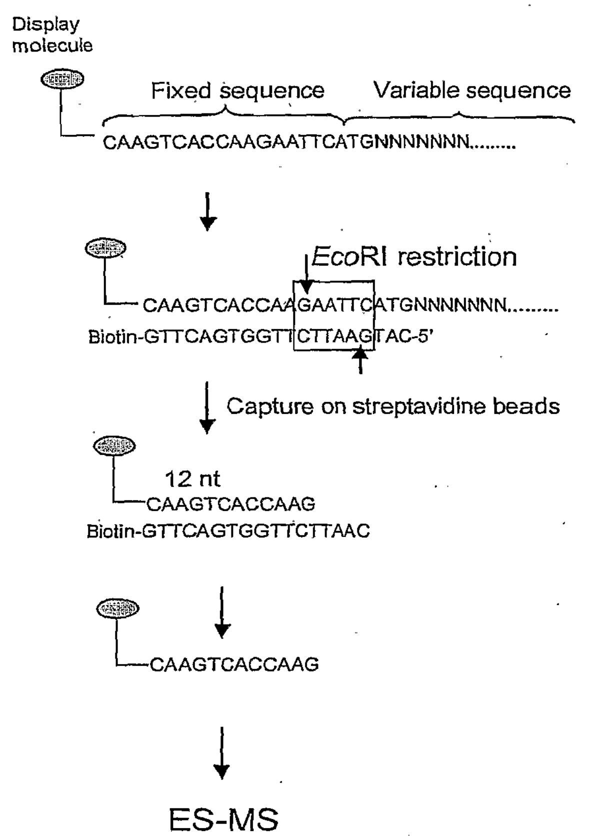
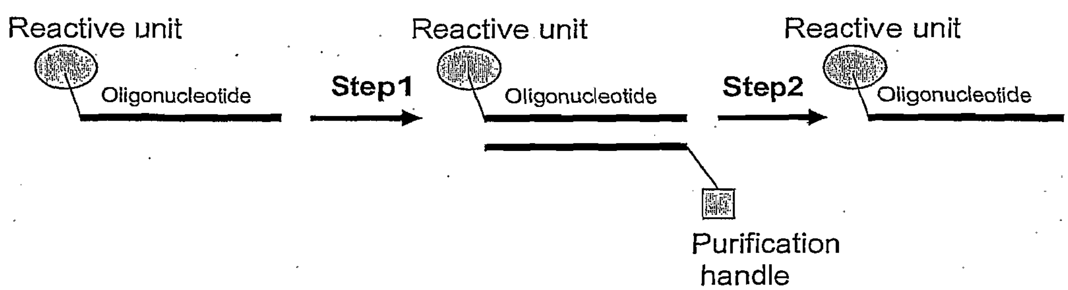


Fig. 55

Library Mimic (general)



Step1: Add oligonucleotide complementary to a control mimic sequence. Purify using handle on complementary oligonucleotide, such as a biotin group, and a suitable method, such as interaction to SA-beads
Step2: Elute mimic and evaluate by analytical tool such as MALDI- or Electrospray MS

Fig. 56

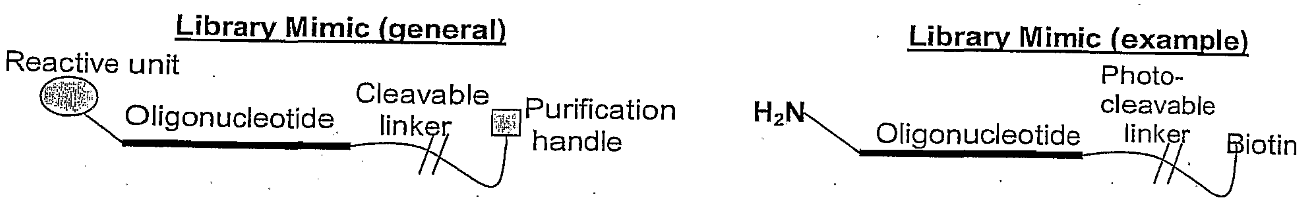

Library Mimic (general)
Reactive unit
Oligonucleotide
Cleavable linker
Purification handle
Library Mimic (example)
H2N
Oligonucleotide
Photo-cleavable linker
Biotin

Fig. 57

Proposed coding strategy for 15 coupling reactions.

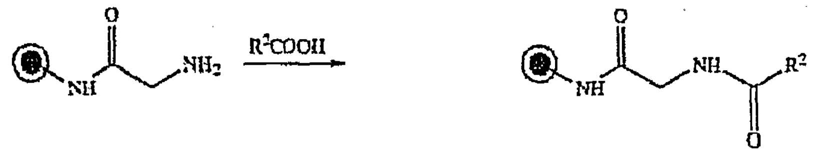
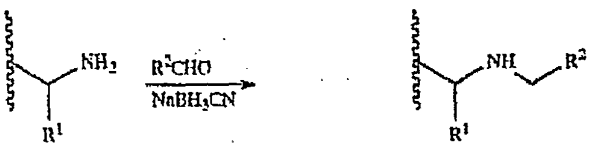
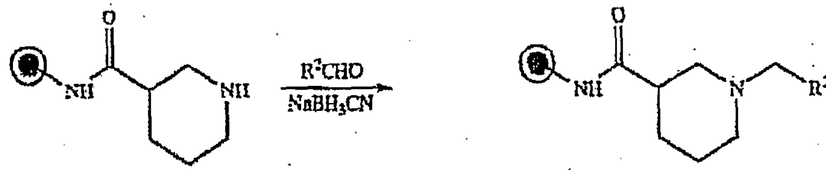
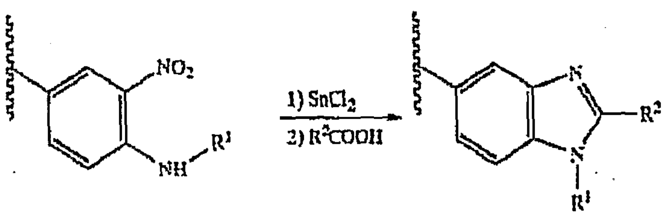
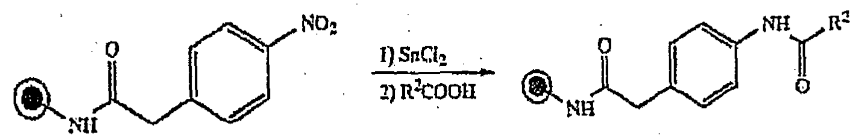
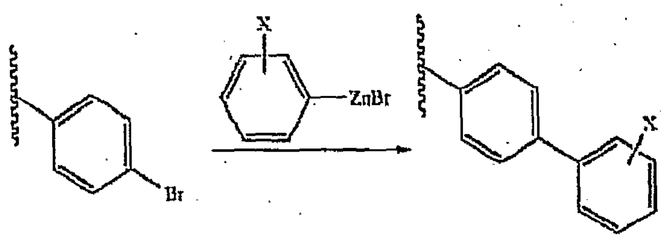
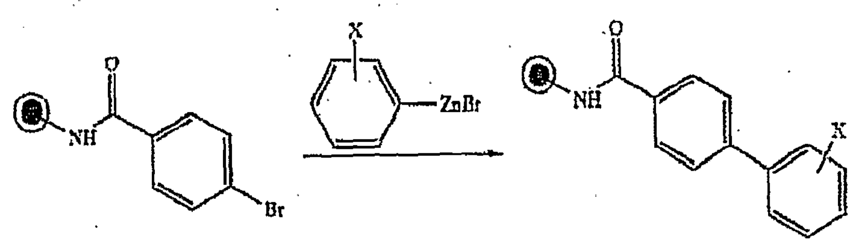
Reaction	Reaction scheme	Reference	Proposed coding reaction
Amine acylation		Perumattam et al. 1998	
Reductive alkylation		Gordon and Steele 1995	
Aromatic reduction, acylation and cyclization		Mazurov 2000	
Aryl-Aryl coupling		Marquais and Arlt 1996	
[3 + 2] Cyclo-addition		Park and Kurth 1999	

Fig. 58

Proposed coding strategy for 15 coupling reactions.

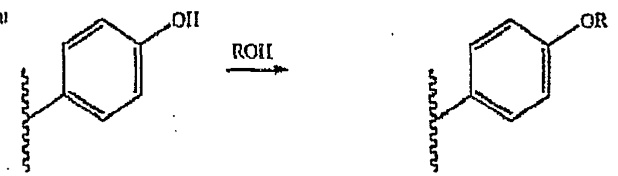
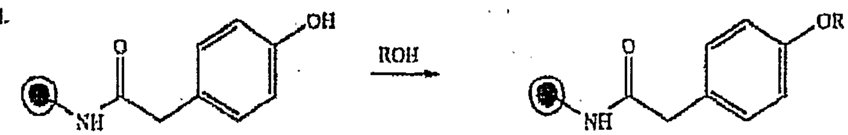
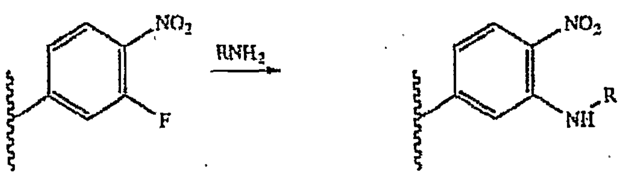
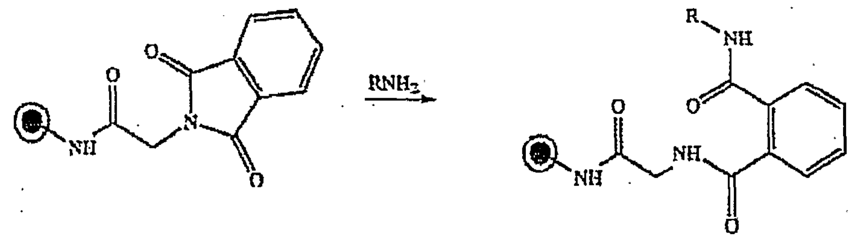
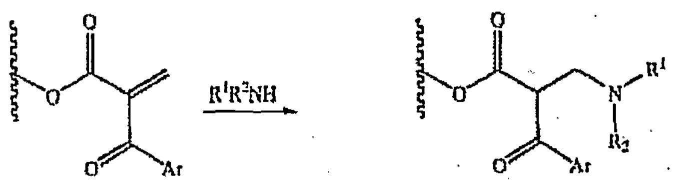
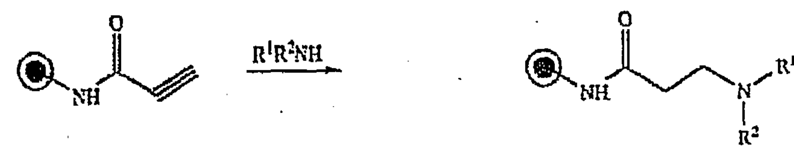
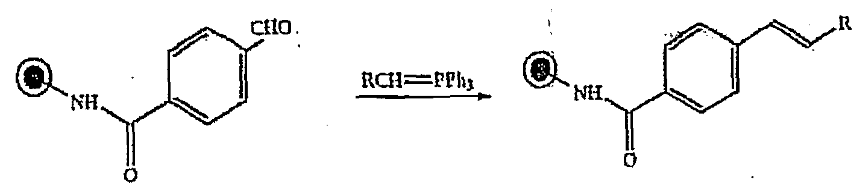
Reaction	Reaction scheme	Reference	Proposed coding reaction
Mitsunobu reaction		Gentles et al. 2002	
Nucleophilic aromatic substitution		Wei and Phillips 1998	
Michael addition		Gnribay et al. 1998	
Wittig reaction		Veerman et al. 1998	

Fig. 58 (cont.)

Proposed coding strategy for 15 coupling reactions.

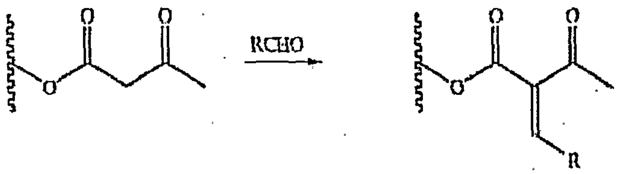
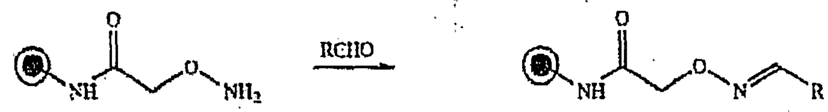
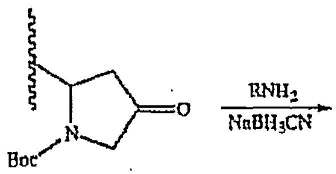
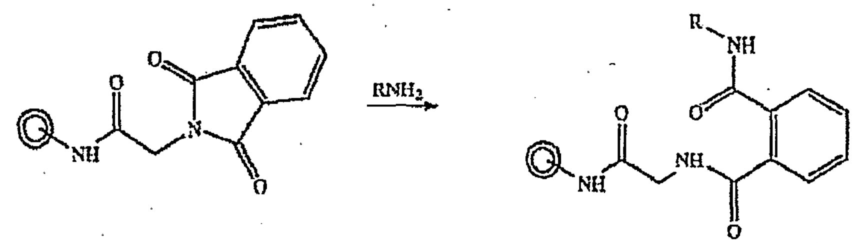
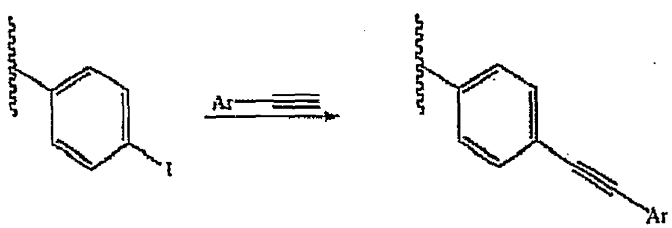
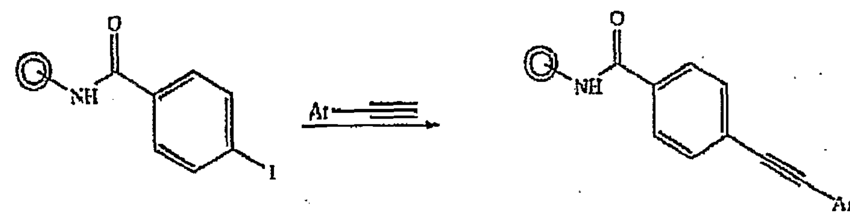
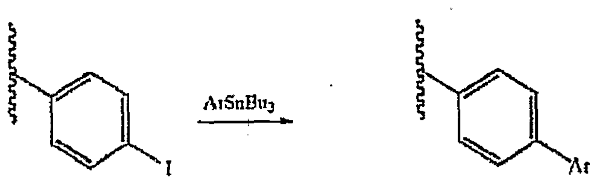
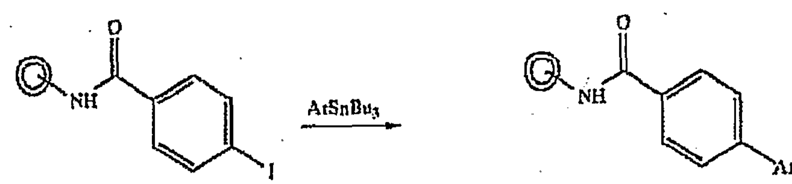
Reaction	Reaction scheme	Reference	Proposed coding reaction
Knoevenagel condensation		Gordeev et al. 1996	
Reductive amination		Bray et al. 1995	
Heck reaction		Yu et al. 1994	
Stille reaction		Forman and Sucholeiki 1995	

Fig. 58 (cont.)

Proposed coding strategy for 15 coupling reactions.

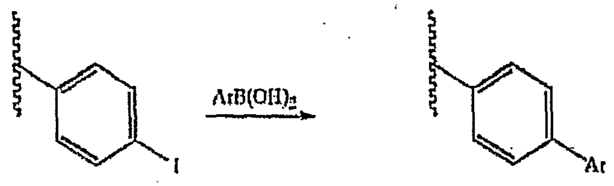
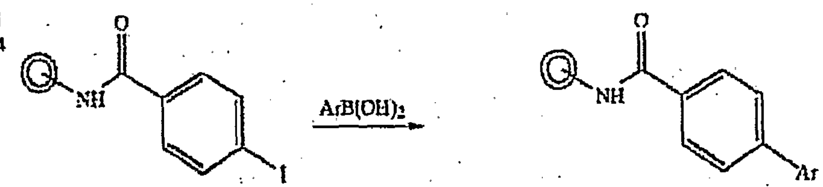
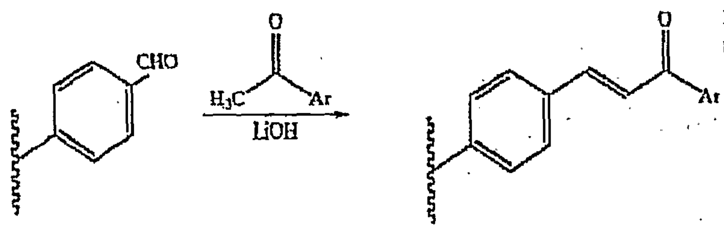
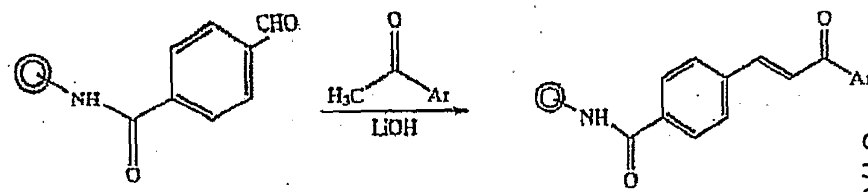
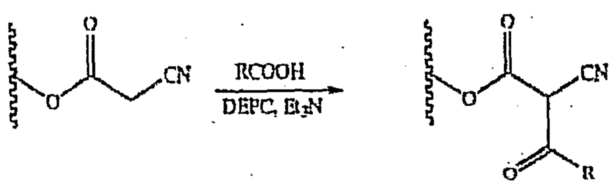
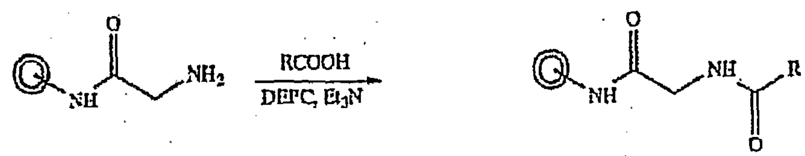
Reaction	Reaction scheme	Reference	Proposed coding reaction
Suzuki reaction		Frenette and Friesen 1994	
Aldol conden-sation		Marzinzik and Felder 1998	
Claisen conden-sation		Sim et al. 1998	

Fig. 58 (cont.)